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(71) Applicant: YAMANOUCHI PHARMACEUTICAL CO. LTD.
No. 3-11 Nihonbashi-Honcho, 2-chome Chuo-ku
Tokyo (JP)

(72) Inventor: Mase, Toshiyasu
81 Maruyama-cho Nijusseikigaoka
Matsudo-chi Chiba (JP)

Hara, Hiromu
5-16-2-505 Mizonuma Danchi Mizunuma
Asaka-shi Saitama (JP)

Nagaoka, Hitoshi
3-16-1 Hasune Itabashi-ku
Tokyo (JP)

Takahasi, Takumi
3-16-1 Hasune Itabashi-ku
Tokyo (JP)

Suzuki, Takeshi
3-16-1 Hasune Itabashi-ku
Tokyo (JP)

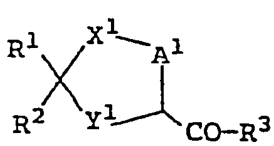
Tomioka, Kenichi
1214-76 Sakata
Okegawa-shi Saitama (JP)

Yamada, Toshimitsu
2-24-12-412 Maeno-cho Itabashi-ku
Tokyo (JP)

(74) Representative: Geering, Keith Edwin et al
REDDIE & GROSE 16 Theobalds Road
London WC1X 8PL (GB)

(54) **Saturated heterocyclic carboxamide derivatives.**

(57) A saturated heterocyclic carboxamide derivative of the following general formula (I) and salts thereof which have platelet activating factor (PAF) antagonizing activity.



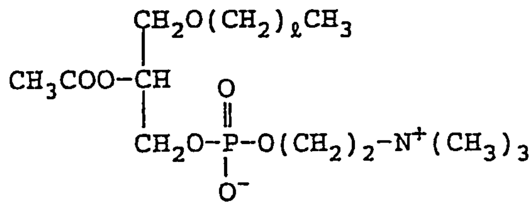
EP 0 279 681 A2

Description

SATURATED HETEROCYCLIC CARBOXAMIDE DERIVATIVES

This invention relates to novel saturated heterocyclic carboxamide derivatives and salts thereof which have platelet activating factor (PAF) antagonizing (anti-PAF) activity.

PAF is a chemical substance released from human and other animal cells and is an acetylglyceryl ether of phosphorylcholine as represented by the following formula

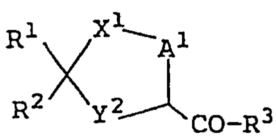


wherein ℓ is the integer 15 or 17.

PAF is physiologically active and causes contraction of the airway smooth muscle, increased vascular permeation, platelet aggregation and blood pressure fall.

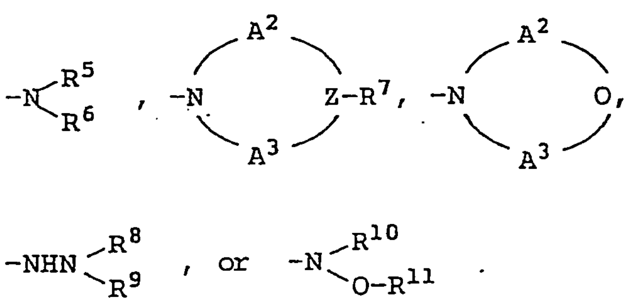
It is thought to be a factor inducing asthma, inflammation, thrombosis, shock and other symptoms. Therefore, studies of substances capable of antagonizing the physiological activities of PAF are under way and several anti-PAF agents have been reported (e.g. European Patent Application No. 178,261 (A), U.S. Patents 4,539,332, 4,656,190, and 4,621,038, European Patent No. 115,979 (B), and British Patent Application No. 2,162,062 (A)).

The invention provides saturated heterocyclic carboxamide derivatives of the following general formula (I),and salts thereof :



(I)

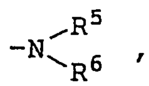
In the above formula (I), R^1 represents a substituted or unsubstituted 5- or 6-membered heterocyclic group which may be condensed with a benzene ring; R^2 represents a hydrogen atom, a lower alkyl group, or an R^1 group defined above; X^1 represents an oxygen or sulfur atom or a methylene group which may be substituted by a lower alkyl group; Y^1 represents an oxygen or sulfur atom or a group of formula $>N-R^4$ wherein R^4 is a hydrogen atom or a lower alkyl, carboxyl, acyl or (lower alkoxy)carbonyl group; A^1 represents a methylene or ethylene group which may be substituted by lower alkyl group(s);R^3 represents a group of formula

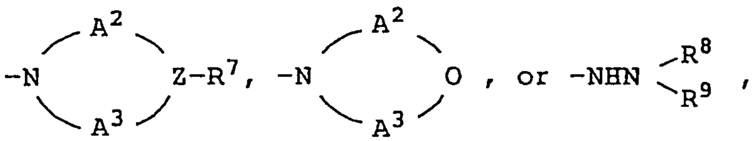


wherein one of R^5 and R^6 is a hydrogen atom or a substituted or unsubstituted hydrocarbon group and the other is a substituted or unsubstituted hydrocarbon group or a substituted or unsubstituted 5- or 6-membered heterocyclic group which may be condensed with a benzene ring, A^2 and A^3 are the same or different and selected from a substituted and unsubstituted lower alkylene groups, Z is a methine group ($>CH-$) or a nitrogen atom, R^7 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group or a carboxyl, acyl, (lower alkoy)carbonyl, carbamoyl, or mono- or di-(lower alkyl)aminocarbonyl group, and R^8, R^9, R^{10} and R^{11} and the same or different, and selected from a hydrogen atom and lower alkyl, aralkyl and aryl groups.

In the above formula (I), it is preferred that R^1 is a pyridyl (optionally in the pyridone form), quinolyl, pyrrolyl, piperidyl, pyrazinyl or furyl group, each of which may be substituted by one or two substituents each selected from lower alkyl, lower alkoxy, (lower alkoxy)carbonyl and dimethylamino groups;

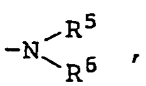
R^2 is a hydrogen atom, a lower alkyl group, or a pyridyl group; X^1 is a sulfur or oxygen atom or a methylene group; Y^1 is an oxygen atom or $>N\text{-}R^4$ wherein R^4 is a hydrogen atom or a lower alkyl, an acyl or a (lower alkoxy)carbonyl group; A^1 is a methylene or ethylene group, which may be substituted by one or two lower alkyl groups; R^3 is

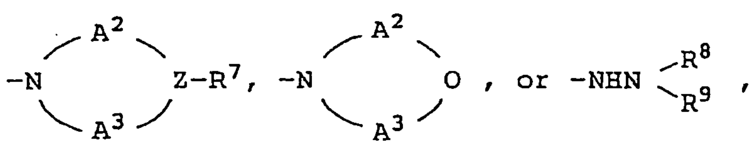




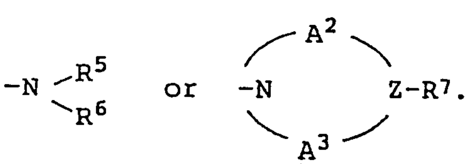
in which one of R^5 and R^6 is a hydrogen atom or a lower alkyl group and the other is a substituted or unsubstituted hydrocarbon group or a substituted or unsubstituted 5- or 6-membered heterocyclic group; A^2 and A^3 are the same or different and selected from substituted and unsubstituted alkylene group; Z is a methine group or a nitrogen atom; R^7 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group, or an acyl, (lower alkoxy)carbonyl, carbamoyl, or mono- or di-alkylaminocarbonyl group; and R^8 and R^9 are the same or different and selected from a hydrogen atom and lower alkyl and aryl groups.

It is more preferred that R^1 is a pyridyl group which may be substituted by one or two substituents selected from lower alkyl, (lower alkoxy) carbonyl and dimethylamino groups; R^2 is a hydrogen atom; X^1 is a sulfur atom; Y^1 is $>N\text{-}R^4$ in which R^4 is a hydrogen atom or a lower alkyl, an acyl or a (lower alkoxy carbonyl group; A^1 is a methylene group which may be substituted by one or two lower alkyl groups; and R^3 is

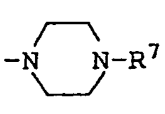




in which one of as defined above, preferably

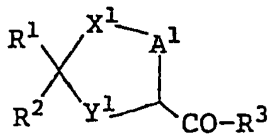


It is particularly preferred that R^1 is a pyridyl group; R^2 is a hydrogen atom; X^1 is a sulfur atom; Y^1 is $>NH$; A^1 is a methylene group; and R^3 is



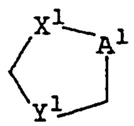
in which R^7 is an aryl-lower alkyl group.

From the chemical structure viewpoint, the compounds of the invention are characterized in that they are saturated heterocyclic carboxamide derivatives whose specific saturated heterocycle is always substituted by a specific heterocycle and a specific carboxamide at respective specific positions. The chemical structure of the compounds according to the invention, which are represented by formula (I)



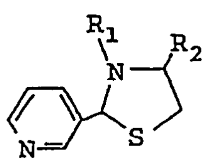
(I)

is characterized in that the saturated heterocycle

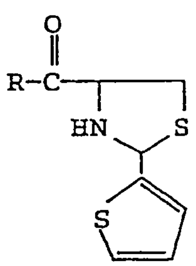


which is a 5- or 6-membered saturated heterocycle is always substituted, at a specific position thereof, by a specific heterocycle, namely the group R^1 which is a 5- or 6-membered heterocycle. which may be condensed with a benzene ring, and, at another specific position, by the group $-COR^3$ which is a specific substituted carboxamide group.

Various saturated heterocyclic carboxamide derivatives similar to the compounds (I) according to the invention have been known so far. For instance, German patent No. 2,729,414 discloses that compounds of the formula



wherein R_1 is an alkanoyl group of 2 to 17 carbon atoms and R_2 is a carboxyl group or an ester or amide thereof, have litholytic activity and U.S. Patent 3,592,905 discloses that compounds of the formula



wherein R is a hydroxy, alkoxy or amino group, have antiinflammatory activity. However, compounds that have the chemical structure characteristics mentioned hereinbefore in accordance with the invention have not been known.

In the definitions of the substituents used herein the term "lower" means, unless otherwise specified, that the relevant group includes a straight or branched carbon chain containing 1 to 6 carbon atoms.

Accordingly, the "lower alkyl group" includes, among others, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2 trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl 1-methylpropyl and 1-ethyl-2-methylpropyl.

The "mono- or di-(lower alkyl)aminocarbonyl group" means a carbamoyl group whose amino group is mono- or di-substituted by the above-mentioned "lower alkyl group or groups" and, more specifically, includes methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl, isobutylaminocarbonyl, pentylaminocarbonyl, isopentylaminocarbonyl, hexylaminocarbonyl, isohexylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, diisopropylaminocarbonyl, dibutylaminocarbonyl, dipentylaminocarbonyl, dihexylaminocarbonyl, ethylmethylamino carbonyl, methylpropylaminocarbonyl, ethylpropylaminocarbonyl, ethylisopropylaminocarbonyl, butylmethylaminocarbonyl and

butylpropylaminocarbonyl, among others.

The term "hydrocarbon group" as used herein means a monovalent group derived from a hydrocarbon, which is a generic name of a compound consisting of carbon and hydrogen atoms, by removal of one hydrogen atom therefrom. preferred examples of the hydrocarbon group are acyclic hydrocarbon groups such as an alkyl group, which is a saturated monovalent hydrocarbon group, and cyclic hydrocarbon groups such as a cycloalkyl group, which is a monocyclic saturated monovalent hydrocarbon group, an aryl group, which is an aromatic monocyclic or polycyclic monovalent hydrocarbon group, a nonaromatic condensed polycyclic hydrocarbon group, and an aralkyl or aralkenyl group, which is a monovalent group derived from an aromatic monocyclic or polycyclic hydrocarbon having a side chain by removal of one hydrogen atom from said side chain.

The "alkyl group" mentioned above is preferably a straight or branched alkyl group containing 1 to 20 carbon atoms and includes, in addition to the above-mentioned examples of the "lower alkyl group", heptyl, 5-methylhexyl, octyl, 6-methylheptyl, nonyl, 7-methyloctyl, decyl, 8-methylnonyl, undecyl, 9-methyldecyl, dodecyl, 10-methylundecyl, tridecyl, 11-methyldodecyl, tetradecyl, 12- methyltridecyl, pentadecyl, 13-methyltetradecyl, hexadecyl, 14-methylpentadecyl, heptadecyl, 15-methylhexadecyl, octadecyl, 16-methylheptadecyl, nonadecyl, 17-methyloctadecyl, eicosyl, 18-methylnonadecyl and so forth.

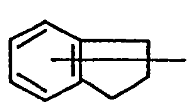
The "cycloalkyl group" preferably contains 3 to 7 carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl,cyclohexyl, cycloheptyl, etc.

Preferred examples of the "aryl group" are phenyl and naphthyl.

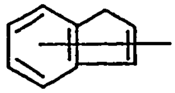
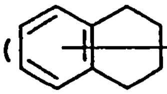
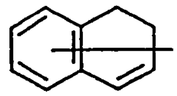
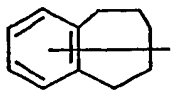
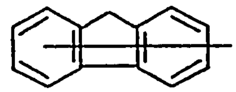
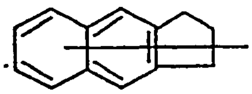
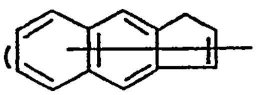
The "aralkyl group" is preferably a group derived from the above-mentioned "lower alkyl group" by substitution of any hydrogen atom by the above-mentioned "aryl group" and includes, among others, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, 1-methyl-2-phenylethyl, 4-phenylbutyl, 3-phenylbutyl, 2-phenylbutyl, 1-phenylbutyl, 2-methyl-3-phenylpropyl, 2-methyl-2-phenylpropyl, 2-methyl-1-phenylpropyl, 1-methyl-3-phenylpropyl, 1-methyl-2-phenylpropyl, 1-methyl-1-phenylpropyl, 1-ethyl-2-phenylethyl, 1,1-dimethyl-2-phenylethyl, 5-phenylpentyl, 4-phenylpentyl, 3-phenylpentyl, 2-phenylpentyl, 1-phenylpentyl, 3-methyl-4-phenylbutyl, 3-methyl-3-phenylbutyl, 3-methyl-2-phenylbutyl, 3-methyl-1-phenylbutyl, 6-phenylhexyl, 5-phenylhexyl, 4-phenylhexyl, 3-phenylhexyl, 2-phenylhexyl, 1-phenylhexyl, 4-methyl-5-phenylpentyl, 4-methyl-4-phenylpentyl, 4-methyl-3-phenylpentyl, 4-methyl-2-phenylpentyl, 4-methyl-1-phenylpentyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 1-(1-naphtyl)ethyl, 1-(2 naphthyl)ethyl, 3-(1-naphthyl)propyl, 3-(2-naphthyl)propyl, 2-(1 naphthyl)propyl, 2-(2-naphthyl)propyl, 1-(1-naphthyl)propyl, 1-(2-naphthyl)propyl, 1-methyl-2-(1-naphthyl)ethyl, 1-methyl-2-(2-naphthyl)ethyl, 4-(1-naphthyl)butyl, 4-(2-naphthyl)butyl, 3-(1-naphthyl)butyl, 3-(2-naphthyl)butyl, 2-(1-naphthyl)butyl, 2-(2-naphthyl)butyl, 1-(1-naphthyl)butyl, 1-(2-naphthyl)butyl, 2-methyl-3-(1-naphthyl)propyl, 2-methyl-3-(2-naphthyl)propyl, 2-methyl-2-(1-naphthyl)propyl, 2-methyl-2-(2-naphthyl)propyl, 2-methyl-1-(1-naphthyl)propyl, 2-methyl-1-(2-naphthyl)propyl, 5-(1-naphthyl)pentyl, 5-(2-naphthyl)pentyl, 4-(1-naphthyl)pentyl, 4-(2-naphthyl)pentyl, 3-methyl-4-(1-naphthyl)butyl, 3-methyl-4-(2 naphthyl)butyl, 6-(1-naphthyl)hexyl, 6-(2-naphthyl)hexyl, 5-(1-naphthyl)hexyl, 5-(2-naphthyl)hexyl, 4-methyl-5-(1-naphthyl)pentyl, 4-methyl-5-(2-naphthyl)pentyl, diphenylmethyl (benzhydryl) and trityl (triphenylmethyl).

The "aralkenyl group" is a group resulting from binding of the above-mentioned "aryl group" to a lower alkenyl group and includes, among others, 2-phenylethyl, 3-phenyl-1-propenyl, 3-phenyl-2-propenyl, 1-methyl-2-phenylbutenyl, 4-phenyl-1-butenyl, 4-phenyl-2-butenyl, 4-phenyl-3-butenyl, 5-phenyl-1-pentenyl, 5-phenyl-2- pentenyl, 5-phenyl-3-pentenyl, 5-phenyl-4-pentenyl, 6-phenyl-1-hexenyl, 6-phenyl-2-hexenyl, 6-phenyl-3-hexenyl, 6-phenyl-4-hexenyl, 6-phenyl-5-hexenyl, 2-(1-naphthyl)ethenyl, 2-(2-naphthyl)ethenyl, 3-(1-naphthyl)-2-propenyl, 3-(2-naphthyl)-2-propenyl, 4-(1-naphthyl)-3-butenyl, 4-(2-naphthyl)-3 butenyl, 5-(1-naphthyl)-2-pentenyl, 5-(2-naphthyl)-2-pentenyl, 5-(1-naphthyl)-4-pentenyl, 5-(2-naphthyl)-4-pentenyl, 6-(1-naphthyl)-2-hexenyl, 6-(2-naphthyl)-2-hexenyl, 6-(1-naphthyl)-5-hexenyl and 6-(2-naphthyl)-5-hexenyl.

Examples of the "nonaromatic condensed polycyclic hydrocarbon group" are indanyl, which may be represented by the formula



which is available for bonding at any optional position on the benzene ring or saturated ring (the same shall apply when the same manner of formula representation is used),

indenyl (e.g. ), tetrahydronaphthyl (), dihydronaphthyl (e.g. ), 1,2-benzo-1-cyclohepten-yl (), fluorenyl (e.g. ), 2,3-dihydro-1H-benz[f]indenyl (), 1H-benz[f]-indenyl (),

and the like condensed polycyclic hydrocarbon groups other than aromatic hydrocarbon groups.

In the compounds of the invention, the "5- or 6-membered heterocyclic group, which may be condensed with a benzene ring", represented by R^1,R^2, R^5,or R^6 is preferably an oxygen-, sulfur- and/or nitrogen-containing, saturated or unsaturated heterocyclic group and, more specifically, includes pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, indolyl, benzimidazolyl, indazolyl, pyridyl, dihydropyridyl, tetrahydropyridyl, piperidinyl, pyrimidinyl, pyridazinyl, pyrazinyl, piperazinyl, quinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, cinnolinyl and other monocyclic or bicyclic, saturated or unsaturated heterocyclic groups containing one or more nitrogen atoms alone as hetero atoms; thiazolinyl, thiazolidinyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzoisothiazolyl and other nitrogen and sulfur atoms-containing, mono- or bicyclic, saturated or unsaturated heterocyclic groups; oxazolyl, oxazolinyl, oxazolidinyl, isoxazolyl, oxadiazolyl, benzoxazolyl, benzisoxazolyl and other nitrogen and oxygen atoms containing, mono- or bicyclic, saturated or unsaturated heterocyclic groups; and, furthermore, heterocyclic groups containing one or more sulfur or oxygen atoms, such as thienyl, tetrahydrothienyl, furyl, tetrahydrofuryl, pyranyl, tetrahydropyranyl, dioxolyl, benzofuryl, benzopyranyl and benzodioxolyl.

These heterocyclic groups are available for bonding at any optional position, either on the heterocycle or on the benzene ring, through a ring-forming carbon atom or a ring-forming nitrogen atom.

The "lower alkylene group" represented by each of A^2 and A^3 is preferably a straight alkylene group containing 1 to 3 carbon atoms and, more specifically, includes methylene, ethylene and trimethylene.

As the "acyl group", there may be made particular mention of lower alkanoyl groups such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl, aralkanoyl groups such as benzylcarbonyl, 3-phenylpropanoyl, 2-phenylpropanoyl, 1-phenylpropanoyl, 4-phenylbutanoyl, 3-phenylbutanoyl, 2-phenylbutanoyl, 1-phenylbutanoyl, 2-methyl-3-phenylpropanoyl, 5-phenylpentanoyl, 4-phenylpentanoyl, 3-phenylpentanoyl, 2-phenylpentanoyl, 1-phenylpentanoyl, 3-methyl-4-phenylbutanoyl, 3-methyl-2-phenylbutanoyl, 6-phenylhexanoyl, 5-phenylhexanoyl, 4-phenylhexanoyl, 3-phenylhexanoyl, 2-phenylhexanoyl, 1-phenylhexanoyl, 4 methyl-5-phenylpentanoyl, 4-methyl-3-phenylhexanoyl and 4-methyl-2- phenylhexanoyl, and substituted or unsubstituted arylcarbonyl groups such as benzoyl, 1-naphthoyl, 2-naphthoyl, (o-, m- or p-)toluoyl, (o-, m- or p-)fluorobenzoyl, (o-, m- or p-)chlorobenzoyl, (o-, m- or p-)bromobenzoyl and various fluoronaphthoyl, chloronaphthoyl and bromonaphthoyl groups. The "(lower alkoxy)carbonyl group" includes, among others, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, 3 methylbutoxycarbonyl, hexyloxycarbonyl and 4-methylpentyloxycarbonyl.

As preferred examples of the "aralkyl group" or "aryl group" represented by any of R^8, R^9, R^{10} and R^{11}, there may be mentioned those aralkyl groups or aryl groups specifically mentioned in relation to the term "hydrocarbon group".

The above-mentioned "hydrocarbon group" and/or "5-or 6-membered heterocyclic group, which may be condensed with a benzene ring" may further have, on any of R^5, R^6, R^7, R^1 and R^2, one or more substituents

each selected from among halogen atoms, lower alkyl groups, hydroxy and related groups (hydroxy, mercapto, alkoxy, lower alkylthio, cycloalkyl-lower alkoxy, cycloalkyl-lower alkylthio, aralkyloxy, aralkylthio, aryloxy, arylthio, aryloxy-lower alkoxy, aryloxy-lower alkylthio, arylthio-lower alkoxy, arylthio-lower alkylthio), oxo and related groups (oxo, thioxo), carboxyl and related groups (carboxyl, (lower alkoxy)carbonyl,acyl), cyano, carbamoyl and related groups (carbamoyl, mono- or di-(lower alkyl)aminocarbonyl), nitro, amino and related groups (amino, mono- or di-(lower alkyl)amino, mono- or diaralkylamino, N-aralkyl-N-lower alkylamino) and, for R^5 or R^6, nitrogen-containing heterocyclic groups.

Preferred as the "halogen atom" is a fluorine, chlorine or bromine atom. The "lower alkyl group" includes those mentioned hereinbefore.

The "alkoxy group" is suitably a straight or branched one containing 1 to 10 carbon atoms and includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy (amyloxy), isopentyloxy, tert-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy, hexyloxy, heptyloxy, 5-methylhexyloxy, octyloxy, 6-methylheptyloxy, nonyloxy, 7-methyloctyloxy, decyloxy, 8-methylnonyloxy, and so on.

The "lower alkoxy group" includes those alkoxy groups mentioned hereinbefore in relation to the "alkoxy group" which contain 1 to 6 carbon atoms.

The "lower alkylthio group" corresponds to the above-mentioned lower alkoxy group in the sense that the former contains a sulfur atom in place of the oxygen atom in the latter. Examples are methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert- butylthio, pentylthio, neopentylthio, 2-methylbutylthio, 1,2 dimethylpropylthio, 1-ethylpropylthio and hexylthio.

The "cycloalkyl-lower alkoxy group" or "cycloalkyl lower alkylthio group" means a group resulting from substitution of one optional hydrogen atom of the above-mentioned "lower alkoxy group" or "lower alkylthio group", respectively, by the above mentioned "cycloalkyl group" and specifically includes, among others, cyclopropylmethoxy (or- methylthio),

2-cyclopropyl-ethoxy (or -ethylthio), 1-cyclopropyl-ethoxy (or -ethylthio), 3-cyclopropyl-propoxy (or -propylthio), 2-cyclopropyl-propoxy (or -propylthio), 1-cyclopropyl-propoxy (or -propylthio), 2-cyclopropyl-1-methyl-ethoxy (or -ethylthio), 4-cyclopropyl-butoxy (or -butylthio), 5-cyclopropylpentyl-oxy (or -thio), 6-cyclopropylhexyl-oxy (or -thio), cyclobutyl methoxy (or-methylthio), 2-cyclobutyl-ethoxy (or -ethylthio), 1-cyclobutyl ethoxy (or ethylthio), 3-cyclobutyl-propoxy (or -propylthio), 2-cyclobutyl-propoxy (or-propylthio), 1-cyclobutylpropoxy (or -propylthio), 2-cyclobutyl-1-methyl-ethoxy (or -ethylthio), 4-cyclobutyl-butoxy (or -butylthio), 5-cyclobutylpentyl-oxy (or -thio), 6-cyclobutylhexyl-oxy (or -thio), cyclopentyl-methoxy (or-methylthio), 2-cyclopentylethoxy (or -ethylthio), 1-cyclopentyl-ethoxy (or -ethylthio), 3-cyclopentyl-propoxy (or -propylthio), 2- cyclopentyl-propoxy (or-propylthio), 1-cyclopentyl-propoxy (or-propylthio), 2-cyclopentyl-1-methyl-ethoxy (or -ethylthio), 4-cyclopentyl-butoxy (or-butylthio), 5-cyclopentylpentyl-oxy (or -thio), 6-cyclopentylhexyl-oxy (or -thio), cyclohexyl-methoxy (or -methylthio), 2-cyclohexyl-ethoxy (or -ethylthio), 1-cyclohexyl-ethoxy (or -ethylthio), 3-cyclohexyl-propoxy (or -propylthio), 2-cyclohexyl-propoxy (or-propylthio), 1-cyclohexyl-propoxy (or-propylthio), 2-cyclohexyl-1-methyl-ethoxy (or -ethylthio), 4-cyclohexylbutyoxy (or-butylthio), 5-cyclohexylpentyl-oxy (or-thio), 6-cyclohexylhexyl-oxy (or -thio), cycloheptyl-methoxy (or -methylthio), 2-cycloheptyl-ethoxy (or -ethylthio), 1-cycloheptyl-ethoxy (or -ethylthio), 3-cycloheptyl-propoxy (or-propylthio), 2-cycloheptyl-propoxy (or-propylthio), 1-cycloheptyl-propoxy (or -propylthio), 2-cycloheptyl-1-methyl-ethoxy (or -ethylthio), 4-cycloheptyl-butoxy (or -butylthio), 5-cycloheptylpentyl-oxy (or -thio) and 6-cycloheptylhexyl-oxy (or-thio).

The "aralkyloxy group" or "aralkylthio group" means a group resulting from substitution of one optional hydrogen atom of the above-mentioned "lower alkoxy group" or "lower alkylthio group" by the above-mentioned "aryl group" and, more specifically, includes the following examples in which the "aryl group" is typified by a phenyl group alone: benzyloxy (or -thio), phenethyl-oxy (or -thio), 1-phenyl-ethoxy (or -ethylthio), 3-phenyl-propoxy (or -propylthio), 2-phenyl-propoxy (or -propylthio), 1-phenyl-propoxy (or -propylthio), 2-phenyl-1-methyl-ethoxy (or -ethylthio), 4-phenyl-butoxy (or -butylthio), 5-phenylpentyl-oxy (or - thio) and 6-phenylhexyl-oxy (or -thio).

Examples of the "aryloxy group" or "arylthio group" are phenoxy (or phenylthio), naphthyl-oxy (or-thio) and other ether or thioether residues derived from aromatic mono- or polycyclic hydrocarbon hydroxy or mercapto compounds.

The "aryloxy-lower alkoxy group", "aryloxy-lower alkylthio group", "arylthio-lower alkoxy group" or "arylthio-lower alkylthio group" means a group resulting from substitution of one optional hydrogen atom of the above-mentioned "lower alkoxy group" or "lower alkylthio group" by the above-mentioned "aryloxy group" or "arylthio group" and, more specifically, includes the following examples wherein the "aryloxy group" or "arylthio group" is typified by a phenoxy (or phenylthio) group alone: phenoxy (or phenylthio)-methoxy (or-methylthio), 2-phenoxy (or phenylthio)-ethoxy (or -ethylthio), 1-phenoxy (or phenylthio)-ethoxy (or -ethylthio), 3-phenoxy (or phenylthio) propoxy (or-propylthio), 2-phenoxy (or phenylthio)-propoxy (or-propylthio), 1-phenoxy (or phenylthio)-propoxy (or-propylthio), 2-phenoxy (or phenylthio)-1-methyl-ethoxy (or -ethylthio), 4-phenoxy (or phenylthio)-butoxy (or -butylthio), 5-phenoxy (or phenylthio)pentyl-oxy (or -thio) and 6-phenoxy (or phenylthio)hexyl-oxy (or-thio).

As examples of the "acyl group" or "mono- or di-(lower alkyl)aminocarbonyl group", there may be mentioned those specific groups that have already been given hereinabove.

The "mono- or di-lower alkylamino group" means a group resulting from substitution of one or two hydrogen atoms of an amino group by "lower alkyl groups" mentioned hereinbefore and, more specifically, includes monoalkylamino groups in which the substituent alkyl group is a straight or branched alkyl group containing 1 to 6 carbon atoms, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, pentylamino, isopentylamino, hexylamino and isohexylamino, symmetrical dialkylamino groups in which the two substituent alkyl groups are the same and each is a straight or branched alkyl group containing 1 to 6 carbon atoms, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, dipentylamino and dihexylamino, and asymmetrical dialkylamino groups in which the two substituent alkyl groups are different from each other and each is a straight or branched alkyl group containing 1 to 6 carbon atoms, such as ethylmethylamino, methylpropylamino, ethylpropylamino, butylmethylamino, butylethylamino and butylpropylamino.

As the "mono- or diaralkylamino group", there may be mentioned monoaralkylamino groups such as benzylamino, phenethylamino, 3-phenylpropylamino, 4-phenylbutylamino, 5-phenylpentylamino, 6-phenylhexylamino, 1-naphthylmethylamino, 2-naphthylmethylamino, 1-naphthylethylamino, 2-naphthylethylamino, 1-naphthylpropylamino, 2-naphthylpropylamino, 1-naphthylbutylamino, 2-naphthylbutylamino, diphenylmethylamino, 2,2-diphenylethylamino, 3,3-diphenylpropylamino, 4,4-diphenylbutylamino and triphenylmethylamino, symmetrical diaralkylamino groups such as dibenzylamino, diphenethylamino, bis(3-phenylpropyl)amino, bis(4-phenylbutyl)amino, bis(5-phenylpentyl)amino and bis(6-phenylhexyl)amino, and asymmetrical diaralkylamino groups such as N-benzylphenethylamino, N-benzyl-3-phenylpropylamino, N-benzyl-4-phenylbutylamino, N-benzyl-5-phenylpentylamino, N-benzyl-6-phenylhexylamino, N-phenethyl-3-phenylpropylamino, N-phenethyl-4-phenylbutylamino, N-phenethyl-5-phenylpentylamino, N-phenethyl-6-phenylhexylamino, N-(3-phenylpropyl)-4-phenylbutylamino, N-(3-phenylpropyl)5-phenylpentylamino, N-(3-phenylpropyl)-6-phenylhexylamino, N-(4-phenylbutyl)-5-phenylpentylamino, N-(4-phenylbutyl)-6-phenylhexylamino and N-(5-phenylpentyl)-6-phenylhexylamino.

The "N-aralkyl-N-lower alkyl group" means a group resulting from substitution of the above-mentioned "lower alkyl group" on the amino group of the above-mentioned "monoaralkylamino group" for rendering the amino group tertiary and typically includes N-methylbenzylamino, N-ethylbenzylamino, N-propylbenzylamino, N-butylbenzylamino, N-pentylbenzylamino, N-hexylbenzylamino, N-methylphenethylamino, N-ethylphenethylamino, N-propylphenethylamino, N-butylphenethylamino, N-pentylphenethylamino, N-hexylphenethylamino, N-methyl-3-phenylpropylamino, N-ethyl-3-phenylpropylamino, N-propyl-3-phenylpropylamino, N-butyl-3-phenylpropylamino, N-pentyl-3-phenylpropylamino, N-hexyl-3-phenylpropylamino, N-methyl-4-phenylbutylamino, N-ethyl-4-phenylbutylamino, N-propyl-4-phenylbutylamino, N-butyl-4-phenylbutylamino, N-pentyl-4-phenylbutylamino and N-hexyl-4-phenylbutylamino.

The "nitrogen-containing heterocyclic group" as a substituent on R^5 and/or R^6 means a saturated or unsaturated, 5- or 6-membered heterocyclic group which contains at least one nitrogen atom as a hetero atom and optionally a sulfur atom and/or an oxygen atom, and may be condensed with a benzene ring. As examples of said group, there may be mentioned those heterocyclic groups containing at least one nitrogen atom as selected from among the examples given hereinbefore as examples of the "5- or 6-membered heterocyclic group, which may be condensed with a benzene ring".

In this case, too, such heterocyclic groups may be available for bonding at any position on the heterocycle or benzene ring either via a ring forming carbon atom or via a ring-forming nitrogen atom, as mentioned hereinabove.

Preferred as the substituent which A^2 and/or A^3 may have are lower alkyl, aralkyl and aryl groups and, in particular, those groups specifically mentioned in relation to the above-mentioned "lower alkyl group" and, in the case of aralkyl and aryl groups, in relation to the "hydrocarbon group".

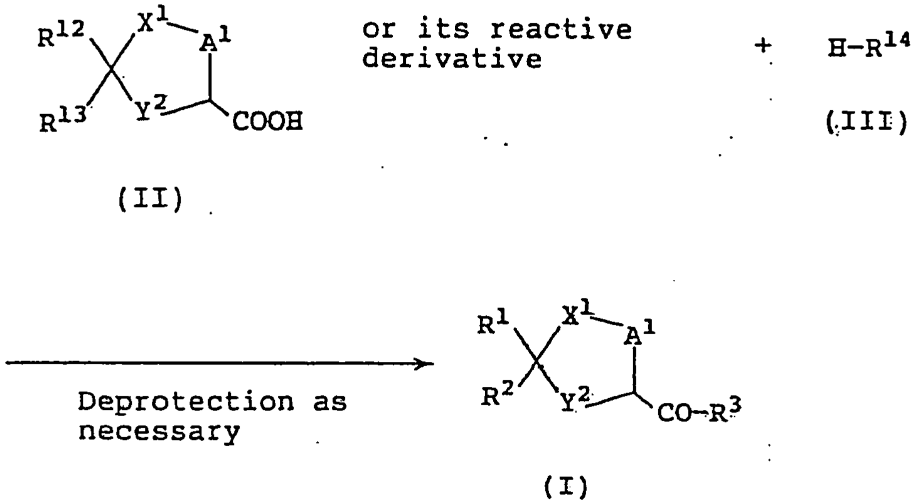
The compounds (I) according to the invention can form salts. The scope of the invention includes salts of the compounds (I). Such salts include acid addition salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid and hydroiodic acid and with organic acids such as acetic acid, oxalic acid, succinic acid, citric acid, maleic acid, malic acid, fumaric acid, tartaric acid, picric acid, methanesulfonic acid and ethanesulfonic acid, salts with acidic amino acids such as glutamic acid and aspartic acid, quaternary ammonium salts resulting from quaternization with alkyl halides such as methyl chloride, methyl bromide and methyl iodide, and so forth.

The compounds (I) provided by the present invention have at least two asymmetric carbon atoms and there can exist isomers due to the presence of such carbon atoms. In certain instances, keto-enol tautomerism may be encountered between a compound having a hydroxy or mercapto group on a heterocycle and a compound having an oxo or thioxo group on a heterocycle. Such isomers all fall within the scope of the present invention either in each individual isolated form or in a mixture form.

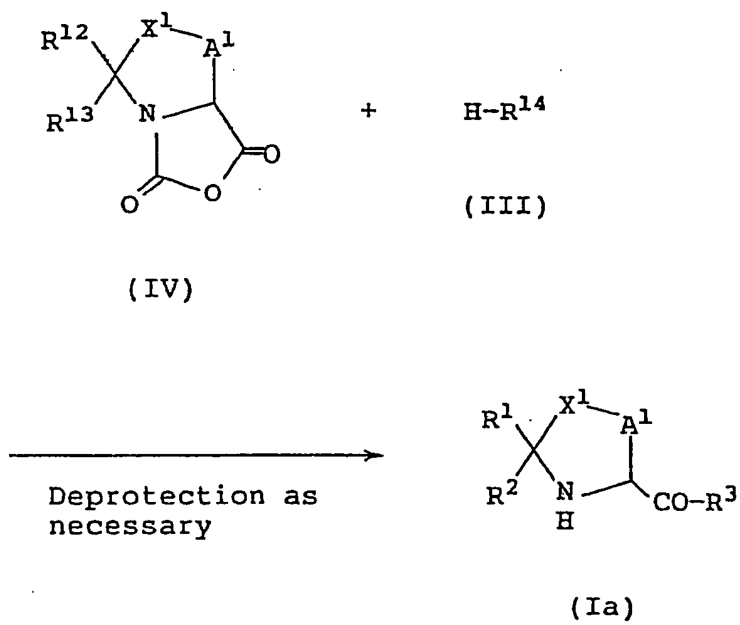
Specific examples of particularly preferred compound (I) and salts thereof in the invention include 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine, 1-decyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine, 1-(4-oxo-4-phenylbutyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine or an acid addition salt thereof, etc., but the present invention should not be construed as being limited thereto.

The compounds (I) according to the invention can be produced by applying various synthetic methods taking advantage of the characteristics of the skeletal structure and various substituents. Typical examples of applicable production processes are given below.

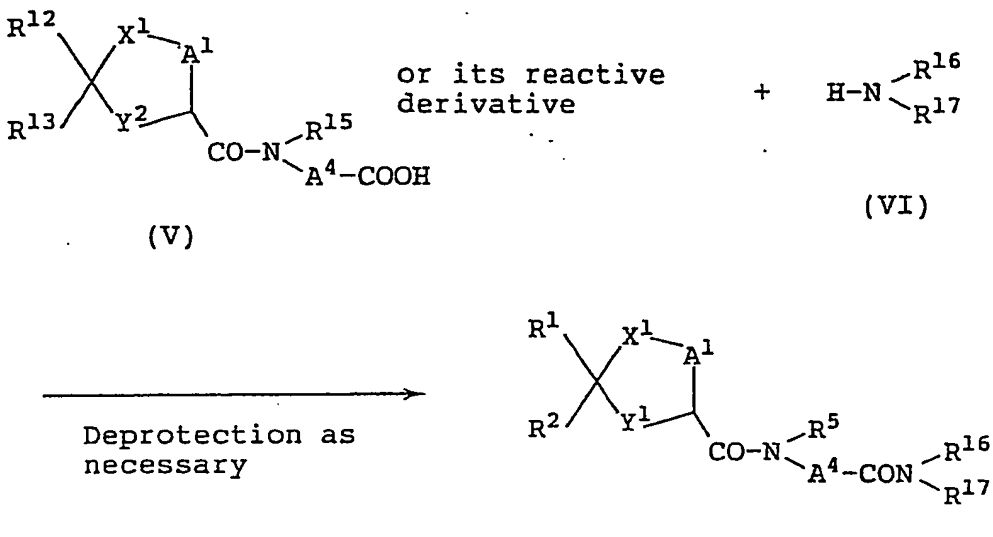
Process 1 (Amidation A)



Process 2 (Amidation B)

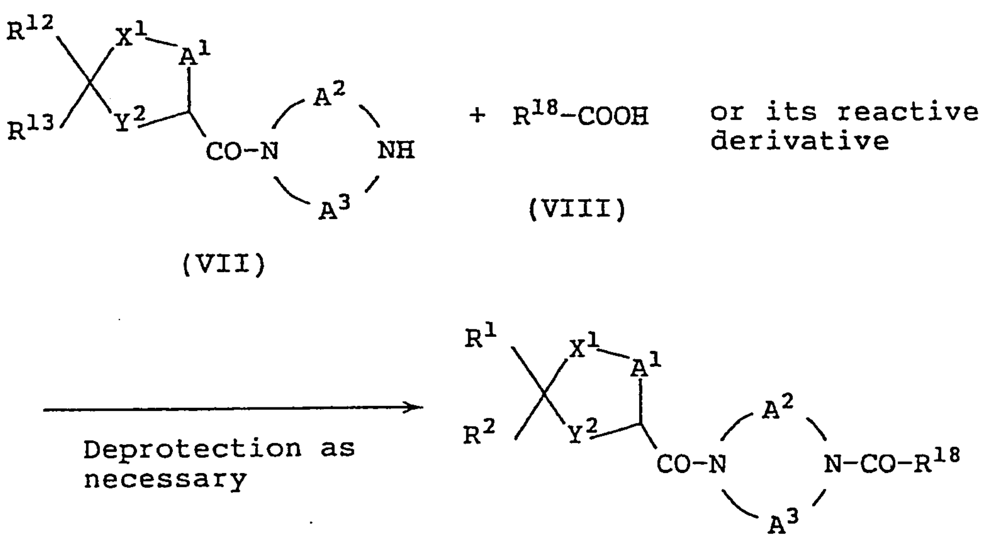


Process 3 (Amidation C)



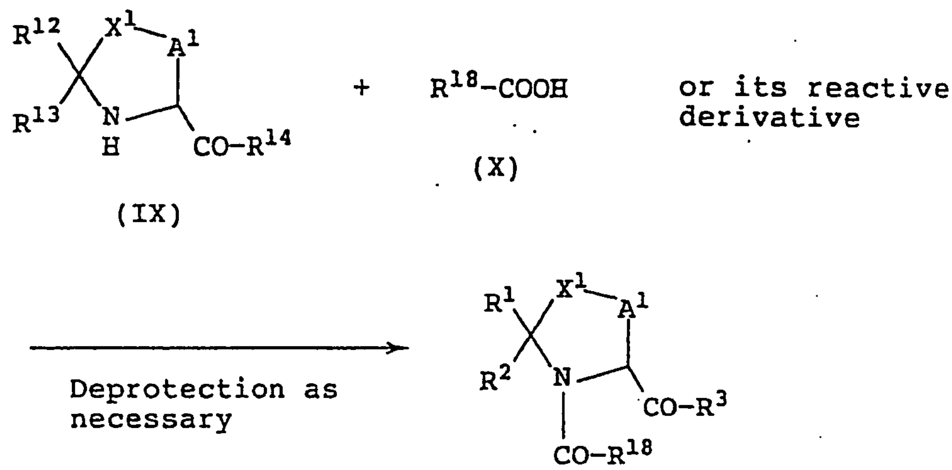
(V) (VI) (Ib)

Process 4 (N-Acylation A)



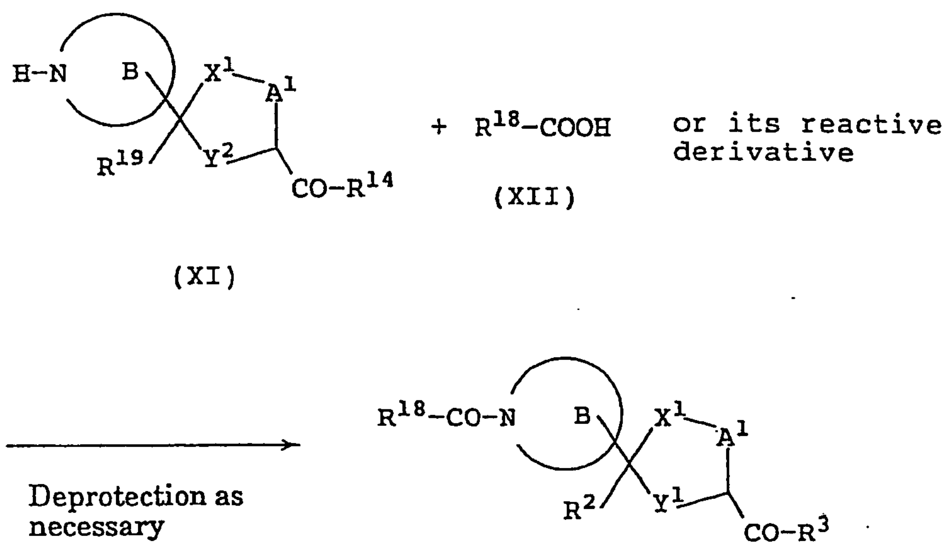
(VII) (VIII) (Ic)

Process 5 (N-Acylation B)



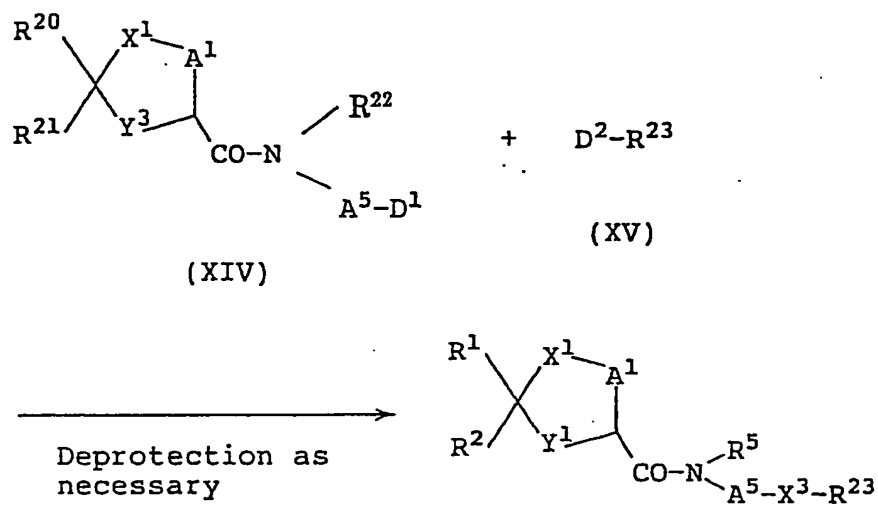
(IX) (X) (Id)

Process 6 (N-Acylation C)



(XI) (XII) (Ie)

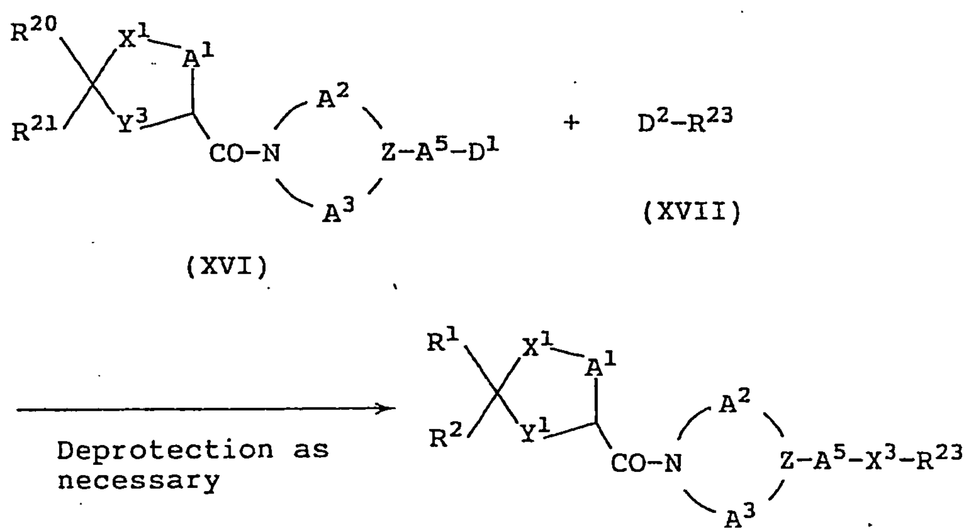
Process 7 (Etherification or thioetherification A)



(XIV) (XV)

(If)

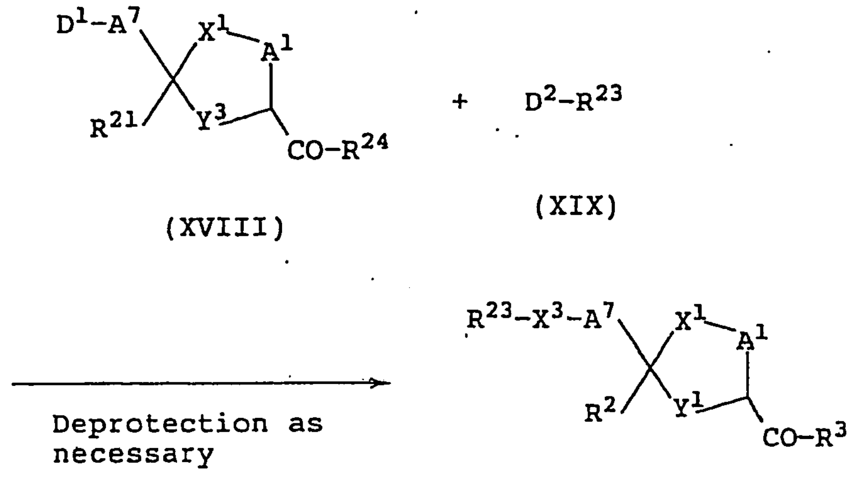
Process 8 (Etherification or thioetherification B)



(XVI) (XVII)

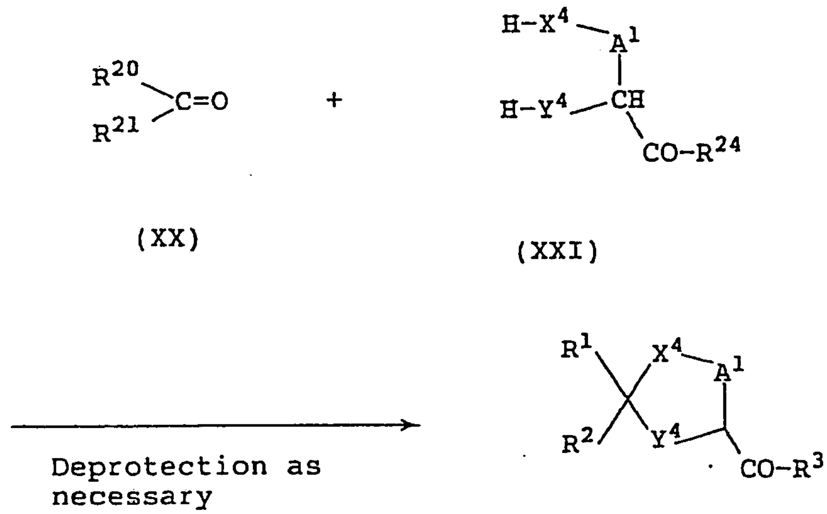
(Ig)

Process 9 (Etherification or thioetherification C)



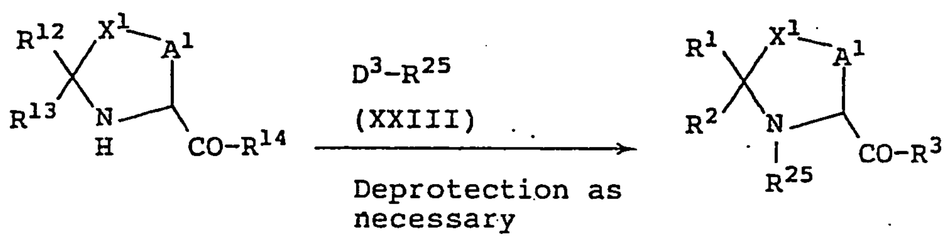
(XVIII) (XIX) (Ih)

Process 10 (Cyclization)



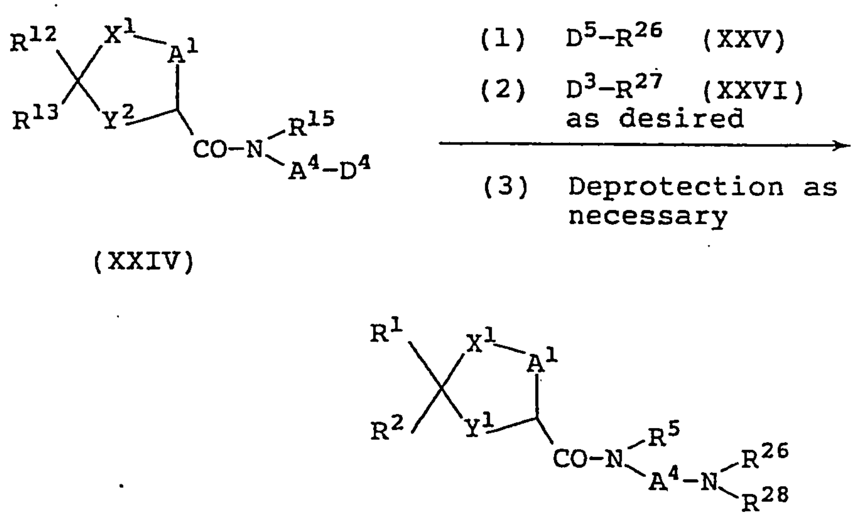
(XX) (XXI) (Ii)

Process 11 (N-Alkylation A)



(XXII) (Ij)

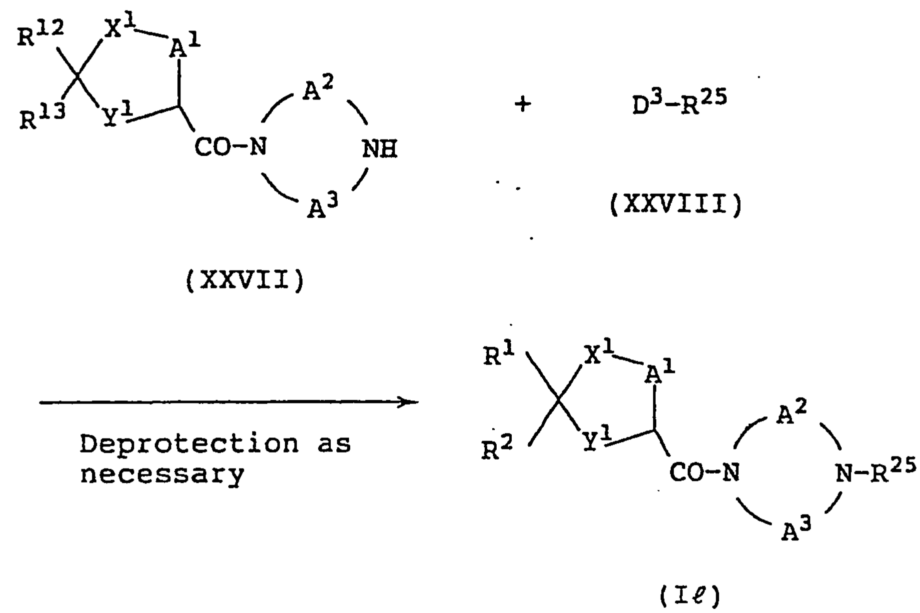
Process 12 (N-Alkylation B)



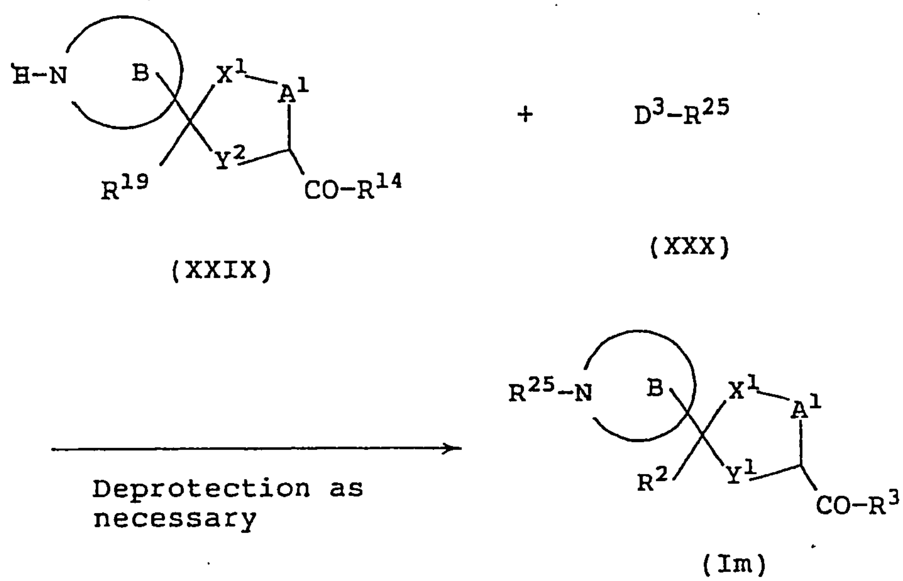
(XXIV)

(Ik)

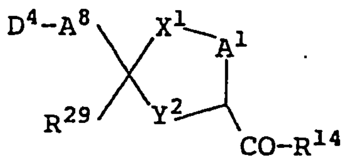
Process 13 (N-Alkylation C)



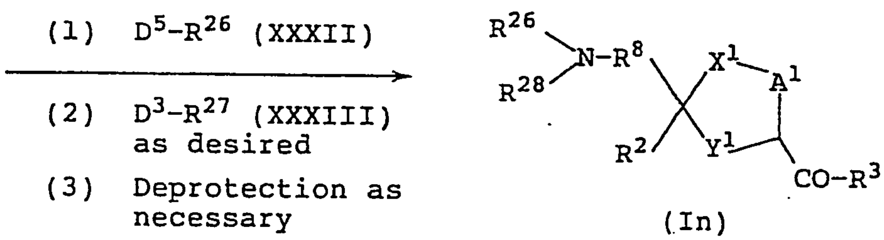
Process 14 (N-Alkylation D)



Process 15 (N-Alkylation E)

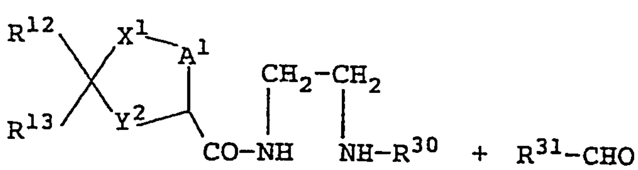


(XXXI)

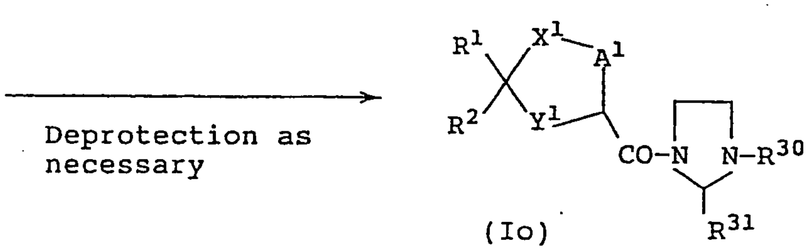


(In)

Process 16

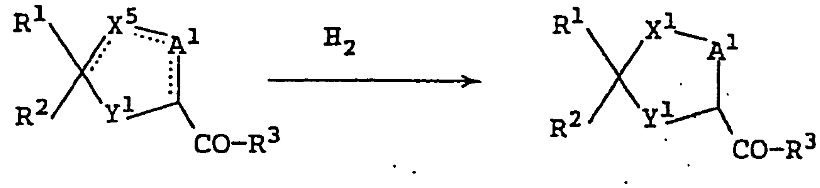


(XXXIV) (XXXV)



(Io)

Process 17 (Reduction)



In the above reaction formulae, R^1, R^2, R^3, R^4, R^5, X^1, A^1, Y^1 and Z each are as defined in above formula (I) and the other substituents are defined as follows:

R^{12}: the same group as R^1, which however may have a protective group;
R^{13}: the same group as R^2, which however may have a protective group;
Y^2: the same group as Y^1, which however may have a protective group;
R^{14}: the same group as R^3, which however may have a protective group;
R^{15}: the same group as R^5, which however may have a protective group;
A^4: a divalent hydrocarbon group;
R^{16} and R^{17}: a hydrocarbon atom or a lower alkyl group; R^{16} and R^{17}, which may be the same or different, a hydrocarbon atom or a lower alkyl group;
R^{18}: the residue of an acyl group after removal of the carbonyl group therefrom;
(N): a nitrogen-containing 5- or 6-membered heterocyclic group in which the nitrogen atom is not a tertiary one and which may be condensed with a benzene ring;
R^{19}: a hydrogen atom, a lower alkyl group or a group of the formula -(N)- ;
R^{20}: the same group as R^1, which however may have a protective group;
R^{21}: the same group as R^2, which however may have a protective group;
Y^3: the same group as Y^1, which however may have a protective group;
R^{22}: the same group as R^5, which however may have a protective group;
A^5: the same group as A^4 or a divalent group of the formula A^4-X^2-A^6-;
X^2: an oxygen atom or a sulfur atom;
A^6: a lower alkylene group;
D^1 and D^2: one is a hydroxy group, a mercapto group, or an alkali metal-substituted hydroxy or mercapto group and the other is a halogen atom or an organo sulfonyloxy group;
R^{23}: an alkyl group of 1 to 10 carbon atoms, a cycloalkyl-lower alkyl group, an aralkyl group, an aryl group, an aryloxy-lower alkyl group or arylthio-lower alkyl group;
X^3: an oxygen atom or a sulfur atom;
A^7: a divalent 5- or 6-membered heterocyclic group, which may be condensed with a benzene ring, or a group of the formula -A^6-X^2-A^6-;
A^8: a divalent 5- or 6 membered heterocyclic group, which may be condensed with a benzene ring;
R^{24}: the same group as R^3, which however may have a protective group;
X^4: an oxygen atom or a sulfur atom;
Y4: an oxygen atom, a sulfur atom or an imino group (-NH-);
D^3: a halogen atom or an organo sulfonyloxy group;
R^{25}: a lower alkyl group, a lower alkoxycarbonyl group or an acyl group;
D^4 and D^5: one is an amino group, which may have a protective group, and the other is a halogen atom or an organo sulfonyloxy group;
R^{26}: a hydrogen atom, a lower alkyl group or an aralkyl group when D^5 is an amino group which may have a protective group; a lower alkyl group or an aralkyl group when D^5 is a halogen atom or an organo sulfonyloxy acid group; D^5-R^{26} may be potassium phthalamide, provided that D^4 is a halogen atom or an organo sulfonyloxy group;
R^{27}: a lower alkyl group or an aralkyl group, which may be the same as or different from R^{26};
R^{28}: a hydrogen atom or the same group as R^{26} or R^{27};
R^{29}: a hydrogen atom, a lower alkyl group or a group of the formula D^4-A^8-;
R^{30}: a hydrogen atom, a lower alkyl group or an aralkyl or an aryl group;
R^{31}: a hydrogen atom, a lower alkyl group, an aralkyl group or an aryl group;
X^5: an oxygen or a sulfur atom, a methylene group which may have a lower alkyl group as a substituent or a methine group which may have a lower alkyl group as a substituent (i.e. H- or lower alkyl-$\overset{|}{C}$= or H- or lower alkyl-$\overset{\|}{C}$-); and
---: one bond is a double bond.

Referring to the above definitions, the protective groups include amino-protecting groups, carboxy-protect-

ing groups, mercapto-protecting groups and hydroxy-protecting groups. As the amino-protecting groups, there may be mentioned urethane-forming protective groups such as benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-methylbenzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-phenylazobenzyloxycarbonyl, p-methoxyphenylazobenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, tert-butoxycarbon yl, tert-amyloxycarbonyl, p-biphenylisopropyloxycarbonyl and diisopropylmethyloxycarbonyl, acyl-type protective groups such as formyl, acyl, trifluoroacetyl, phthalyl, tosyl, o-nitrophenylsulfenyl, p-methoxy-o-nitrophenylsulfenyl, benzoyl and chloroacetyl, alkyl-type protective groups such as trityl, benzyl, 2-benzoyl-1-methylvinyl and trimethylsilyl, and allylidene type protective groups such as benzylidene and 2 hydroxy-allylidene.

As the carboxy-protecting groups, there may be mentioned ester residues such as benzyl, p-nitrobenzyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, methyl, ethyl, tert-butyl, benzhydryl, trityl, phthalimidomethyl, cyclopentyl, 2-methylthioethyl, phenacyl and 4-picolyl.

As the mercapto-protecting groups, there may be mentioned benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl, trityl, benzyloxycarbonyl, benzoyl, ethylcarbamoyl, acetamidomethyl, ethylthio, benzylthiomethyl, and so forth. As the hydroxy-protecting groups, there may be mentioned benzyl, tert-butyl, acetyl, trifluoroacetyl, benzyloxycarbonyl, and so on.

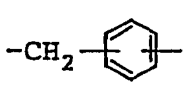
The "divalent hydrocarbon group" corresponds to the substituted hydrocarbon group in R^5, R^6 or R^7 and preferably is an alkylene group, a cycloalkanediyl group, an arylene group, a divalent nonaromatic condensed polycyclic hydrocarbon group, an aralkylene group or an aralkenylene group.

The "alkylene group" preferably contains 1 to 20 carbon atoms, which may be straight or branched and, more specifically, includes, among others, methylene, methylmethylene, ethylene, trimethylene, propylene, tetramethylene, 1-methyltrimethylene, 2-methyltrimethylene, 3-methyltrimethylene, pentamethylene, 1-methyltetramethylene, 4-methyltetramethylene, hexamethylene, 5-methylpentamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene, dodecamethylene, tridecamethylene, tetradecamethylene, pentadecamethylene, hexadecamethylene, heptadecamethylene, octadecamethylene, nonadecamethylene and eicosamethylene.

The "cycloalkanediyl group" includes various cyclopropanediyl groups, various cyclobutanediyl groups, various cyclopentanediyl groups, various cyclohexanediyl groups and various cycloheptanediyl groups.

As the "divalent nonaromatic condensed polycyclic hydrocarbon group", there may be mentioned various indanediyl groups, various indenediyl groups, various tetrahydronaphthalenediyl groups, various dihydronaphthalenediyl groups, various 1,2-benzo-1-cycloheptenediyl groups, various fluorenediyl groups, various 2,3-dihydro-1H-benz[f]indenediyl groups and various 1H-benz[f]indenediyl groups, among others.

As the "arylene group", there may be mentioned phenylene groups (o-, m- and p-). various naphthalenediyl groups, and so forth. The "aralkylene group" means a divalent group of an arylalkene as resulting from bonding of the above-mentioned "arylene group" to a lower alkylene group containing 1 to 6 carbon atoms and is, for example,



when the arylene group is phenylene and the lower alkylene group is methylene.

As the alkali metal atom for forming an alcoholate (phenolate) or thiolate (thiophenolate), there may be mentioned potassium and sodium, among others.

As said "residue of an acyl group after removal of the carbonyl group therefrom", lower alkyl groups, aralkyl groups, halo-substituted or unsubstituted aryl groups and lower alkoxy groups are particularly preferred. As specific examples of such groups, there may be mentioned those mentioned hereinbefore.

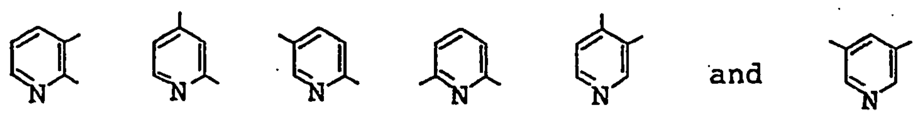
The "nitrogen-containing 5- or 6-membered heterocyclic group in which the nitrogen atom is not a tertiary one and which may be condensed with a benzene ring" means a group which belongs to the class of the "5- or 6-membered heterocyclic group, which may be condensed with a benzene ring" as represented by R^1 and/or R^2 and contains at least one nitrogen atom and in which at least one nitrogen atom is not yet a tertiary one. Examples of such group are thus as follows: 1H-pyrrolyl, Δ^2- or Δ^3- pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 4H-1,2,4-triazolyl, 1H-1,2,3,4-tetrazolyl, indoyl, benzimidazolyl, 1H-indazolyl, 2H-indazolyl, 1,4-dihydropyridyl, tetrahydropyridyl, piperidinyl, piperazinyl, Δ^4-thiazolinyl, thiazolidinyl, Δ^4-oxazolinyl, oxazolidinyl, Δ^4-isoxazolinyl and isoxazolidinyl.

The "halogen atom" represented by D^1, D^2, D^3, D^4 or D^5 is, for example, an iodine, bromine or chlorine atom, whereas the "organo sulfonyloxy group" is, for example, an alkylsulfonyloxy group such as methanesulfonyloxy or ethnesulfonyloxy, a benzenesulfonyloxy, or an arylsulfonyloxy group such as toluene- (in particular p-toluene-)sulfonyloxy group.

The "cycloalkyl-lower alkyl group" represented by R^{25} indicates a group resulting from substitution of one optional hydrogen atom of the above-mentioned "lower alkyl group" by the above-mentioned "cycloalkyl group". Thus, for instance, when the lower alkyl group is methyl and the cycloalkyl group is cyclohexyl, said group is cyclohexylmethyl.

Similarly, the "aryloxy-lower alkyl group" or "arylthio-lower alkyl group" means a group resulting from substitution of one optional hydrogen atom of the above-mentioned "lower alkyl group" by the above-mentioned "aryloxy group" or "arylthio group", respectively. Thus, for instance, when the lower alkyl group is propyl and the aryloxy or arylthio group is phenoxy (or phenylthio), the group in question is phenoxy-(or phenylthio-)propyl.

The "divalent 5- or 6-membered heterocyclic group, which may be condensed with a benzene ring" as represented by A^7 and/or A^8 corresponds to the "5- or 6-membered heterocyclic group, which may be condensed with a benzene ring" as represented by R^1 and/or R^2. Thus, more specifically, for the pyridine ring, there may be mentioned various pyridinediyl groups, namely pyridine-2,3-diyl, pyridine-2,4 diyl, pyridine-2,5-diyl, pyridine-2,6-diyl, pyridine-3,4-diyl and pyridine-3,5-diyl, respectively represented by:



The other groups are as already mentioned in the above formula (I).

The production processes are now described in more detail.

Process 1

The compounds (I) of the invention can be produced by reacting heterocyclic carboxylic acid of general formula (II), which may have a protective group, or reactive derivative thereof, with amine of general formula (III), which may have a protective group, if necessary followed by deprotecting (removing the protective group or groups).

As the reactive derivative of compound (II), there may be mentioned acid halides such as acid chloride and acid bromide; acid azide; active esters with N-hydroxybenzotriazole, N-hydroxysuccinimide, etc.; symmetric acid anhydride; and acid anhydrides with alkylcarbonic acids, p-toluenesulfonic acid, etc.

When the compound (II) is used in the free carboxylic acid form, it is advantageous to carry out the reaction in the presence of a condensing agent such as dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole.

The reaction conditions may vary to some extent depending on starting compound, particularly on the kind of reactive derivative of compound (II). Generally, however, it is advantageous to carry out the reaction in an organic solvent inert to the reaction, such as pyridine, tetrahydrofuran, dioxane, ether, N,N-dimethylformamide, benzene, toluene, xylene, methylene chloride, dichloroethane, chloroform, ethyl acetate or acetonitrile, using the starting compounds (II) and (III) in equimolar amounts or using one of them in excess.

According to the kind of reactive derivative, or when the starting (III) is used in a salt form, it is in some instances advantageous to carry out the reaction in the presence of a base, for example an organic base such as trimethylamine, triethylamine, pyridine, picoline, lutidine, dimethylaniline or N-methylmorpholine, or an inorganic base such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide or potassium hydroxide. It is also possible to promote the reaction by using the starting compound (III) in excess. Pyridine can serve also as a solvent.

The reaction temperature may vary, hence should suitably be selected, depending on the kind of said reactive derivative.

It is favorable to the reaction that a mercapto group, a reactive amino group, a carboxyl group and a hydroxy group be absent. It is possible, however, to obtain desired compounds having such groups by means of protective group introduction prior to reaction and deprotection after reaction.

The method of deprotection may vary depending on the protective group.

For instance, when substituted or unsubstituted benzyloxycarbonyl is used as an amino-protecting group, the deprotection is preferably carried out by catalytic reduction and in certain instances by acid treatment with hydrobromic acid/acetic acid, hydrobromic acid/trifluoroacetic acid, hydrofluoric acid, etc. other urethane-forming protective groups, e.g. tert-butoxycarbonyl, can advantageously be removed by acid treatment using hydrobromic acid/acetic acid, trifluoroacetic acid, hydrochloric acid, hydrochloric acid/acetic acid, hydrochloric acid/dioxane, etc.

When methyl or ethyl is used as a carboxy-protecting group, deprotection can easily be effected by saponification. Benzyl and various substituted benzyl groups as carboxy-protecting groups can be eliminated with ease by catalytic reduction or saponification. carboxy-protecting tert butyl can easily be removed by the same acid treatment as mentioned above, and trimethylsilyl group by contact with water.

Mercapto- or hydroxy protecting groups can be removed in most cases by treatment with sodium liquid ammonia or with hydrofluoric acid. In some cases (e.g. o-benzyl, o-benzyloxycarbonyl, s-p-nitrobenzyl), they can be removed also by applying catalytic reduction. when they are acyl groups, they can be eliminated by treatment with an acid or alkali.

The deprotection treatments mentioned above can be performed in conventional manner.

Process 2

Those compounds of general formula (Ia) in which Y^1 is an imino group can be produced also by reacting oxazolidinedione ring-condensed heterocyclic compound of general formula (IV) with compound (III).

Compound (IV) is a compound in which the C-terminus of compound (II) is in an activated form and at the same time the amino group of compound (II) is in a protected form. Hence, the reaction also fall under the category of amidation.

In respect to reaction conditions, protective groups and methods of deprotection, this process is substantially the same as Process 1.

Process 3

The compounds of the invention include those amide compounds in which R^3 is an amino group substituted by a hydrocarbon group having a carbamoyl, mono or di- (lower alkyl)aminocarbonyl group. Such compounds, which are represented by general formula (Ib), can be produced by reacting side chain carboxylic acid of general formula (V) or reactive derivative thereof with amine of general formula (VI), if necessary followed by deprotecting.

In respect of reaction conditions and so forth, this process is substantially the same as Process 1.

Process 4

The compounds of the invention which have the general formula (Ic) can be produced by reacting corresponding cyclic secondary amine (VII) with carboxylic acid of general formula (VIII) or a reactive derivative thereof, if necessary followed by deprotecting.

This N-acylation reaction can be carried out in the same manner as in Process 1.

Process 5

Those compounds of the invention which are represented by the general formula (Id) can be produced by reacting corresponding heterocyclic secondary amine (IX) with carboxylic acid of general formula (X) or a reactive derivative thereof, if necessary followed by deprotecting.

The reaction conditions and the like are substantially the same as in Process 1.

Process 6

The compounds of the invention include those compounds (Ie) in which R^1 (or R^1 and R^2 each) is a heterocyclic group containing a cyclic secondary amine-forming nitrogen atom with an acyl group bonded to the nitrogen atom. They can be produced by reacting compound (XI) with compound (XII) or reactive derivative thereof in the same manner as in Process 1.

Process 7

The compounds of the invention include ether or thioether compounds. Such compounds can be produced by applying a conventional method of etherification or thioetherification.

Among the conventional methods, the most general method which comprises reacting an alcohol or mercaptan or an alkali metal derivative thereof with a halide or sulfonate can be used most advantageously.

Thus, the ether or thioether compounds of general formula (If) can be produced by reacting hydroxy or mercapto compound of general formula (XIV) or alkali metal derivative thereof with halide or sulfonate compound of general formula (XV), or reacting halide or sulfonate compound of general formula (XIV) with hydroxy or mercapto compound of general formula (XV) or alkali metal derivative thereof.

The reaction is carried out in an organic solvent such as N,N-dimethylformamide, dimethyl sulfoxide, acetone, methyl ethyl ketone (2-butanone), methanol, ethanol, ethylene chloride, chloroform, ether, tetrahydrofuran or dioxane, or water, or in a mixed solvent composed of water and such an organic solvent, using the compounds (XIV) and (XV) in substantially equimolar amounts or using either of them in slight excess.

When the starting hydroxy or mercapto compound (XIV) or (XV) is not in the alkali metal-substituted form, the reaction is carried out in the presence of a base, preferred examples of which are sodium hydroxide, potassium hydroxide, sodium hydride, sodium carbonate, potassium carbonate and Triton B.

Although the reaction temperature is not critical, the reaction is usually carried out at room temperature or with heating.

When the starting compound (XIV) contains an additional free or alkali metal-substituted mercapto group, thioetherification generally takes place simultaneously on the group.

According to the kind of substituent, it is preferable to carry out the reaction after introduction of a protective group so that the expected side reaction can be inhibited. In that case, postreaction deprotection can be effected by treating in the same manner as described in relation to Process 1.

Process 8

The ether or thioether compounds of general formula (Ig) can be produced by reacting compound (XVI) with compound (XVII). The reaction conditions and the like are the same as in Process 7.

Process 9

The ether or thioether compounds of general formula (Ih), too, can be produced by reacting and treating in the same manner as in Process 7 with compound (XVIII) and compound (XIX) as the starting compounds.

Process 10

Among the compounds of the invention, those compounds (Ii) in which X^1 is an oxygen or sulfur atom can be produced by applying a cyclization or ring closure reaction using ketone (or aldehyde) of general formula (XX) and diol, dithiol, hydroxy-mercaptan, amino-alcohol or amino-mercaptan compound of general formula (XXI) as the starting compounds.

The reaction is carried out in a solvent such as an alcohol (e.g. methanol, ethanol, isopropanol) or an aqueous alcohol and generally at room temperature using the compounds (XX) and (XXI) in almost equimolar amounts or using either of them in slight excess. It is also possible to conduct the reaction while removing by-product water as an azeotrope with such a solvent as benzene or toluene using a Dean-Stark trap or the like. It is favorable to this reaction that additional reactive groups such as mercapto, amino and carboxyl are absent. Protection of such groups, however, renders the reaction practicable. In that case, deprotection can be effected in the same manner as in Process 1.

Process 11

The N-substituted compounds of general formula (Ij) can be produced by reacting corresponding cyclic secondary amine of general formula (XXII) with halide or sulfonate of general formula (XXIII), if necessary followed by deprotecting.

When the starting compound (XXIII) is a halide, the reaction is advantageously carried out in a solvent such as mentioned above for Process 7, at room temperature or with heating or refluxing, using the compounds (XXII) and (XXIII) in approximately equimolar amounts or using either of them in slight excess.

In some instances, the addition of a secondary or tertiary base such as pyridine, picoline, N,N-dimethylaniline, N-methylmorpholine, trimethylamine, triethylamine or dimethylamine or of an inorganic base such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide or potassium hydroxide can advantageously cause the reaction to proceed smoothly.

When the starting compound (XXIII) is a compound substituted by an organo sulfonyloxy group, the reaction is advantageously carried out in a solvent such as mentioned above in relation to Process 7, with cooling or at room temperature, using the compounds (XXII) and (XXIII) in approximately equimolar amounts or using either of them in slight excess. The reaction period should be selected with due consideration of various reaction conditions.

The absence of such groups as mercapto, reactive carboxyl and reactive hydroxy group is favorable to this reaction, too. However, protective group introduction prior to the reaction makes it possible to obtain desired compounds. When there is additionally a reactive amino group, the amino group may also be subject to simultaneous N-alkylation. In that case, it is possible to obtain desired compounds when an easily eliminable protective group is introduced prior to the reaction and is removed after reaction.

Deprotection can be effected as described above for Process 1.

Process 12

Those compounds of the invention in which R^3 is a diamine type substituent can be produced by applying the method comprising reacting amine of general formula (XXIV) with halide or sulfonate of general formula (XXV) or reacting halide or sulfonate of general formula (XXIV) with amino (XXV).

When symmetrically disubstituted amino compounds are produced, one of the compounds (XXIV) and (XXV) is used in an amount of about 2 moles per mole of the other, as the case may be preferably, the compound (XXIV) is an amine and the compound (XXV) is a halide or sulfonate, and the halide or sulfonate compound (XXV) is used in an amount of about 2 moles per mole of the amine compound (XXIV). When the desired compounds are monosubstituted amines or when disubstituted amines are to be produced using monosubstituted amines as starting materials, both the reactants are used in approximately equimolar amounts. Other reaction conditions, such as solvent, temperature, addition of base and deprotection conditions, are substantially the same as in Process 11.

In producing monosubstituted amines as the desired compounds, it is desirable to inhibit tertiary amine formation so that the desired products can be produced in good yields. For that purpose, the amino group of D^4 or D^5 should preferably be converted in advance to a secondary amine form by introducing a protective group for preventing tertiary amine formation, such as toluenesulfonyloxy, acetyl, phenacylsulfonyl, trifluoromethanesulfonyl or bisbenzenesulfonyl.

When primary amines are to be produced by using a halide or sulfonate compound (XXIV) in which D^4 is a halogen atom or an organo sulfonyloxy group as one starting material, the compound (XXV) may be an ammonia. It is advantageous, however, to apply the method comprising carrying out the reaction using the potassium salt of phthalimide and thereafter removing the protective group.

Process 13

Those compounds of the invention which have the general formula ($I\ell$) can be produced by reacting corresponding cyclic secondary amine (XXVII) with compound (XXVIII). The reaction conditions and so forth

are approximately the same as in Process 11.

Process 14

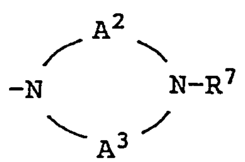
The compounds (Im) can be derived from the starting compounds (XXIX) and (XXX) in the same manner as in Process 11.

Process 15

Those compounds of the invention which have the formula (In) and have an amino group, or a mono- or disubstituted amino group on R^1 and/or R^2 can be produced by treating the reactants in the same manner as in Process 12.

Process 16

For producing those compounds (Io) of the invention in which R^3 is the group



forming a 5-membered ring, namely imidazolidine compounds, various methods of synthesizing 1,3-diazoles are applicable. Among them, an advantageous method of producing the compounds (Io) comprises subjecting to ring closure or cyclization corresponding ethylenediamine compound (starting compound) of general formula (XXXIV) in which one of the two ethylenediamine nitrogen atoms is in an amide form. While various carbonyl compounds can be used as ring closure reagents, aldehyde of general formula (XXXV) is preferred when the introduction of a hydrocarbon-derived substituent is taken into consideration.

The reaction can be effected by heating the compounds (XXXIV) and (XXXV) in an inert organic solvent (e.g. toluene) with a molecular sieve added.

While the absence of additional reactive groups such as mercapto, amino, carboxyl in the starting compounds is favorable to the reaction, a starting compound can be submitted to the reaction without difficulty when said group is protected beforehand, as the case may be. In that case, deprotection can be carried out in the same manner as in Process 1.

Process 17

Among the compounds of the invention, there are various compounds which can be obtained by reduction (e.g. reduction of C=C to C-C, C≡C to C=C or C-C, NO_2 to NH_2, S-S to SH).

In the process given above by way of example, the basic saturated heterocycle skeletons of the compounds according to the invention are formed by reduction of the corresponding unsaturated or incompletely hydrogenated heterocycles.

The reduction is advantageously carried out catalytically in the presence of a reduction catalyst such as platinum black, platinum oxide, palladium-on-carbon or Raney nickel.

Other production processes

In the foregoing, detailed mention has been made of amidation, etherification or thioetherification, cyclization and N-alkylation reactions, among others. However, the compounds of the invention contain various functional groups and therefore can be produced by applying various methods selected according to the characteristics of such groups.

For instance, the compounds (I) of the invention which have a free carboxyl group as a substituent can be produced from corresponding esters by eliminating the ester residue by a conventional method. Conversely, those compounds which have a lower alkoxycarbonyl group, an esterified carboxyl group, as a substituent can be produced by reacting a corresponding carboxylic acid or a reactive derivative thereof with a lower alcohol or a reactive derivative thereof such as a lower alkyl halide in the conventional manner for ester formation.

The thus-produced compounds (I) of the invention are isolated in the free form or in the form of salts thereof and purified. The salts can be produced by subjecting the free-form compounds to a conventional salt formation reaction.

Isolation and purification can be performed by applying ordinary procedures in chemistry, such as extraction, concentration, crystallization, filtration, recrystallization and various forms of chromatography.

As already mentioned hereinabove, the compounds of the invention may occur as optical isomers such as racemic modifications, optically active substances and diastereomers, geometric isomers, namely cis and trans forms, and tautomeric isomers, namely keto and enol forms, either singly or in the form of a mixture. Stereochemically pure isomers can be obtained by using appropriate starting compounds or by using a general method of optical resolution [e.g. the method which comprises conversion to diastereomer salts with an optically active acid in general use (e.g. tartaric acid)]. Separation of diastereomer mixtures can be realized in conventional manner, for example by fractional crystallization or chromatography. Geometric isomers can

be separated from each other by utilizing a difference in physicochemical property therebetween.

The compounds (I) and salts thereof according to the invention have PAF-antagonizing activity and are useful in the treatment and prevention of various diseases caused by PAF. In particular, they can be used as antiasthmatics, antiinflammatory agents, antiulcer agents, shock symptom alleviating agents, therapeutic agents for ischemic heart and brain diseases, liver diseases, thrombosis and nephritis, rejection inhibitors for use in organ transplantation, etc.

Some of the compounds of the invention have vasodilating activity and such compounds are useful as vasodilators as well.

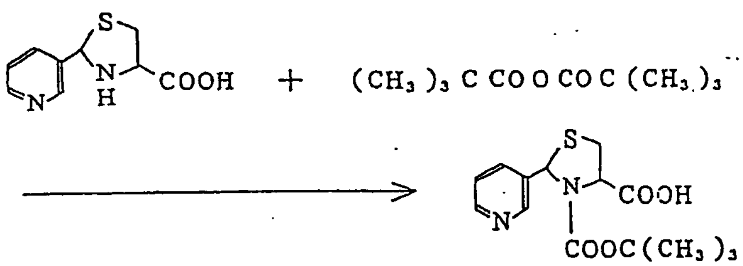
The compounds of this invention shown by the general formula (I) or the salts thereof can be orally or parenterally administered as they are or as medical compositions composed of these compounds and pharmaceutically permissible carriers or excipients (e.g., tablets, capsules, powders, granules, pills, ointments, syrups, injections, inhalants, suppositories, etc.). The dose depends upon the patients, administration routes, symptoms, etc., but is usually 0.1 to 500 mg, preferably 1 to 200 mg per adult per day and is orally or parenterally administered in 2 or 3 sub doses per day.

The following examples are further illustrative of the present invention.

The above-mentioned starting compounds contain novel compounds and their production are described in the reference examples.

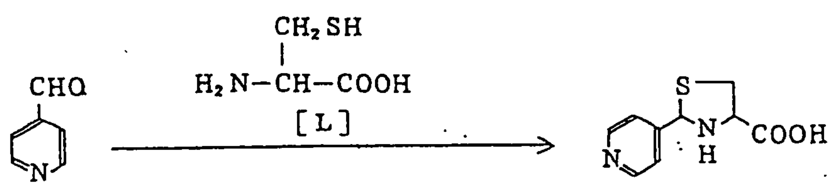
In the following, NMR indicates a nuclear magnetic resonance spectrum with TMS as an internal standard, MS mass spectrum, LAH lithium aluminum hydride, HOBT 1-hydroxybenzotriazole, DCC dicyclohexylcarbodiimide, THF tetrahydrofuran, and DMF N,N-dimethylformamide.

REFERENCE EXAMPLE 1



Di-tert-butyl dicarbonate (2.4 g) and 10 ml of 1 N aqueous sodium hydroxide were added to a mixture of 2.1 g of 2-(3-pyridyl)thiazolidine-4-carboxylic acid (prepared from L-cysteine and pyridine-3-carbaldehyde), 20 ml of water and 40 ml of dioxane at a temperature not higher than 4°C, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, 30 ml of water was added, the pH was adjusted to 2 to 3 by addition of 0.5 M aqueous citric acid, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate to give 1 g of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid. Melting point 167°-169°C.

REFERENCE EXAMPLE 2

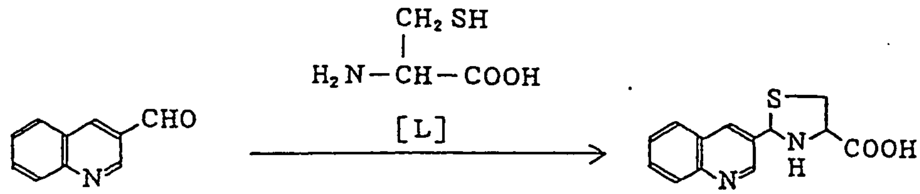


Pyridine-4-carbaldehyde (1.07 g) and 1.21 g of L-cysteine were heated in 60% ethanol at a refluxing temperature for 4 hours. Activated charcoal (100 mg) was added to the reaction mixture while it was warm. The mixture was filtered. After cooling, the resultant crystalline precipitate was collected by filtration and washed with ethanol to give 1.2 g of 2-(4-pyridyl)thiazolidine-4-carboxylic acid. melting point 171-173°C.

NMR ($DMSO-d_6$)

δ: 3.0~3.5 (2H), 3.9~4.2 (1H, 5.56 and 5.78 (s, respectively 1H), 7.4~7.6 (2H), 8.5~8.6 (2H)

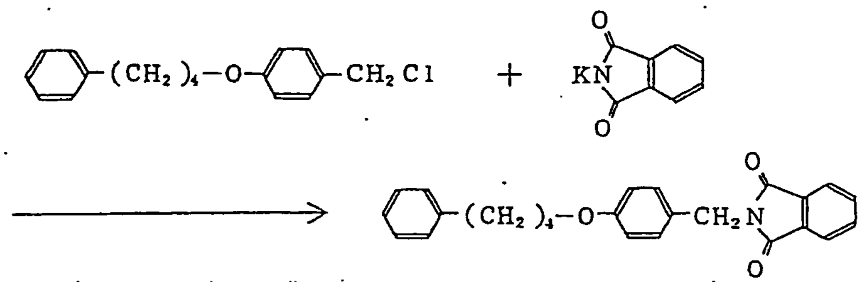
REFERENCE EXAMPLE 3



Quinoline-3-carbaldehyde (1.57 g) and 1.21 g of L-cysteine were dissolved in 50 ml of 50% ethanol, and the solution was stirred at room temperature for 1 hour. The resultant crystalline precipitate was collected by suction filtration, washed with 50% ethanol and dried to give 1.95 g of 2-(3-quinolyl)thiazolidine-4 carboxylic acid. Melting point 173-175°C (decomposition).

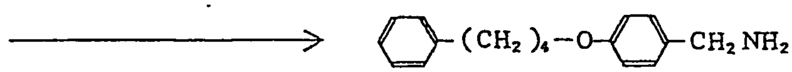
REFERENCE EXAMPLE 4

(1)



A solution of 1.20 g of p-chloromethyl-(4-phenylbutoxy)benzene and 1.15 g of potassium phthalimide in 20 ml of N,N-dimethylformamide was stirred at 100°C for 3 hours. The reaction mixture was diluted with ethyl acetate, and the dilution was washed with three portions of water and then with saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residual solid was recrystallized from ethyl acetate to give 1.85 g of N-[p-(4-phenylbutoxy)benzyl]phthalimide. Melting point 106-107.5°C.

(2)

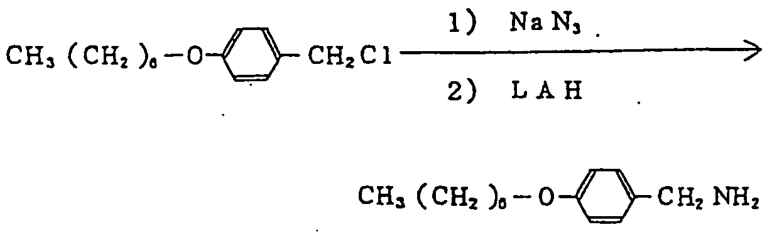


A solution of 920 mg of N-[p-4-phenylbutoxy)benzyl]phthalimide obtained in (1) and 200 mg of hydrazine hydrate in 10 ml of ethanol was refluxed for 3 hours. After cooling, the solid precipitate was filtered off, and the filtrate was concentrated. Chloroform was added to the residue, and the insoluble matter was filtered off. The filtrate was concentrated to give 190 mg of p-(4-phenylbutoxy)benzylamine.

NMR ($CDCl_3$)

δ:1.6~1.9 (4H, 2.5~2.8 (2H), 3.75 (2H, br), 3.8~4.0 (2H), 6.7~6.9 (2H), 7.1~7.3 (7H)

REFERENCE EXAMPLE 5



A solution of 1.25 g of sodium azide in 2.5 ml of water was added to a solution of 900 mg of p-chloromethyl(heptyloxy)benzene in 25 ml of N,N-dimethylformamide, and the mixture was stirred at 100°C for 6 hours. After cooling, the reaction mixture was diluted with water, and the product was extracted with ether. The ether layer was washed in sequence with water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. A solution of the thus-obtained residual oil in 10 ml of tetrahydrofuran was added dropwise at 0°C over 5 minutes to a suspension of 200 mg of lithium aluminum hydride in 15 ml of tetrahydrofuran. The resultant mixture was stirred at the same temperature for 1 hour and then at room temperature for 1 hour. Then, sodium sulfate decahydrate added to decompose the excess lithium aluminum hydride. The insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure to give 860 mg of p-heptyloxybenzylamine.

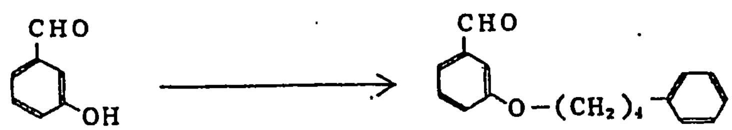
MS: m/z 221 (M^+)

NMR ($CDCl_3$)

δ: 0.8~1.0 (3H), 1.2~1.5 (10H), 1.6~1.9 (2H), 3.80 (2H, s), 3.94 (2H, t), 6.87 (2H, d), 7.22 (2H, d)

REFERENCE EXAMPLE 6

(1)



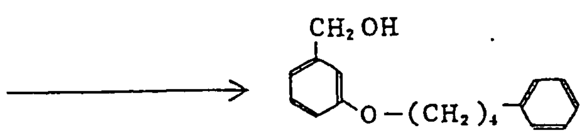
A solution of 380 mg of m-hydroxybenzaldehyde, 600 mg of 1-bromo-4-phenylbutane and 580 mg of potassium carbonate in 3 ml of N,N-dimethylformamide was stirred overnight at room temperature. After dilution with ethyl acetate, the reaction mixture was washed with water, 1 N sodium hydroxide, water and saturated aqueous solution of sodium chloride, in that order, and then dried over anhydrous magnesium sulfate. The ethyl acetate layer was concentrated under reduced pressure to give 660 mg of m-(4-phenylbutoxy)benzaldehyde.

MS: m/z 254 (M^+)

NMR ($CDCl_3$)

δ:1.6~1.9 (4H), 2.6~2.8 (2H), 4.06 (2H, t), 7.2~7.4 (9H), 9.96 (1H, s)

(2)

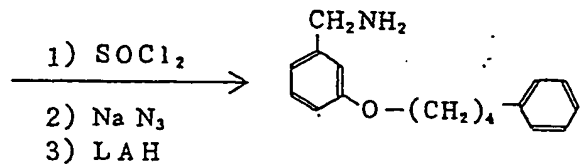


Sodium borohydride (200 mg) was added to a solution of 660 mg of m-(4-phenylbutoxy)benzaldehyde in 10 ml of methanol, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, 5% hydrochloric acid was added to the residue, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 510 mg of m-(4-phenylbutoxy)benzyl alcohol.

NMR ($CDCl_3$)

δ: 1.6~1.9 (4H), 2.6~2.8 (2H), 3.9~4.1 (2H), 4.60 (2H, s), 7.2~7.5 (9H)

(3)



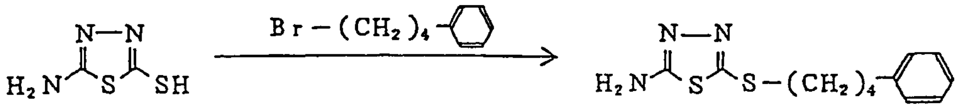
m-(4-Phenylbutoxy)benzyl alcohol (510 mg) was dissolved in 5 ml of benzene, 1.4 g of thionyl chloride was added, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure to give 520 mg of m chloromethyl-(4-phenylbutoxy)benzene. This compound was then treated by the procedure of Reference Example 4 to give 470 mg of m-(4-phenylbutoxy)benzylamine.

MS: m/z 255 (M^+)

NMR ($CDCl_3$)

δ:1.6~1.9 (4H, 2.6~2.8 (2H), 3.6~3.9 (2H), 3.9~4.1 (2H), 6.7~6.9 (3H), 7.2~7.4 (6H)

REFERENCE EXAMPLE 7

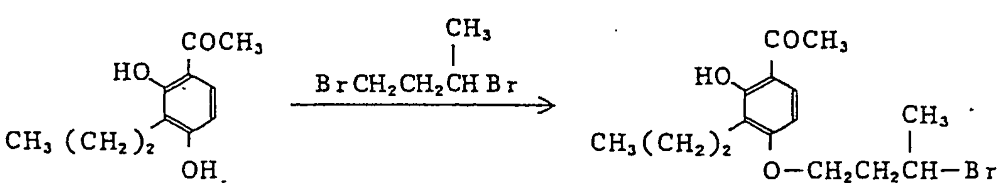


A solution of 320 mg of 2-amino-5-mercapto-1,3,4-thiadiazole, 430 mg of 1-bromo-4-phenylbutane and 350 mg of potassium carbonate in 5 ml of N,N-dimethylformamide was stirred overnight at room temperature. After dilution with ethyl acetate, the reaction mixture was washed in sequence with water, 1 N sodium hydroxide, water and saturated aqueous solution of sodium chloride, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was recrystallized from ethyl acetate to give 300 mg of 2-amino-5-[(4-phenylbutyl)thio]-1,3,4-thiadiazole. Melting point 111°C.

Elemental analysis (for $C_{12}H_{15}N_3S_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	54.31	5.70	15.83	24.16
Found:	54.29	5.69	15.88	23.90

REFERENCE EXAMPLE

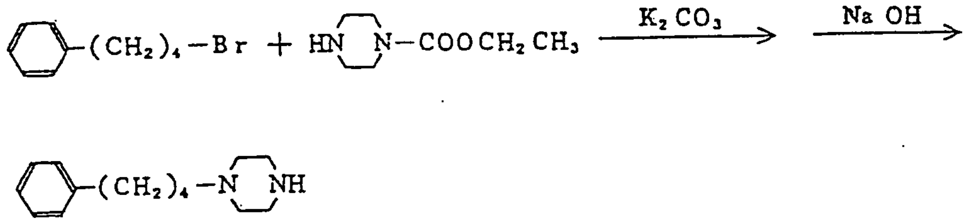


A mixture of 5.0 g of 2,4-dihydroxy-3-propylacetophenone, 11.1 g of 1,3-dibromobutane, 6.0 g of potassium carbonate and 50 mg of tetra-n-butylammonium bromide in 130 ml of acetone was refluxed overnight. After cooling, the insoluble matter was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate=8:1) to give 2.47 g of 1-[4-(3-bromobutoxy)-2-hydroxy-3-propylphenyl]ethanone. Melting point 53-55°C.

Elemental analysis (for $C_{15}H_{21}O_3Br$):

	C (%)	H (%)	Br (%)
Calculated:	54.72	6.43	24.27
Found:	54.98	6.40	23.91

REFERENCE EXAMPLE 9



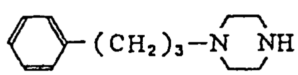
A solution of 2.47 g of 1-bromo-4-phenylbutane in 5 ml of 2-butanone was added to a mixture of 1.93 g of 1-ethoxycarbonylpiperazine, 1.76 g of potassium carbonate and 15 ml of 2-butanone at room temperature. After stirring at 80°C for 12 hours, the mixture was cooled and, after addition of water, extracted with ethyl acetate. The extract was washed with water and saturated aqueous solution of sodium chloride in that order and dried over anhydrous sodium sulfate. The residue obtained after concentration under reduced pressure was purified by silica gel column chromatography (eluent: hexane-ethyl acetate = 4:1) to give 1-ethoxycarbonyl-4-(4-phenylbutyl)piperazine. The compound obtained was dissolved in 20 ml of ethanol and 20 ml of 10% aqueous solution of sodium hydroxide, and the solution was stirred at 100°C for 12 hours. After cooling, the reaction mixture was extracted with ethyl acetate, and the extract was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluent: chloroform-methanol-25% aqueous ammonia = 100:10:1) to give 1.5 g of 1-(4-phenylbutyl)piperazine as an oil.

NMR ($CDCl_3$)

δ: 1.34 ~ 1.85 (4H, m), 2.20 ~ 3.04 (12H, m), 7.04 ~ 7.40 (5H, m)

MS: m/z 217 (M^+)

REFERENCE EXAMPLE 10



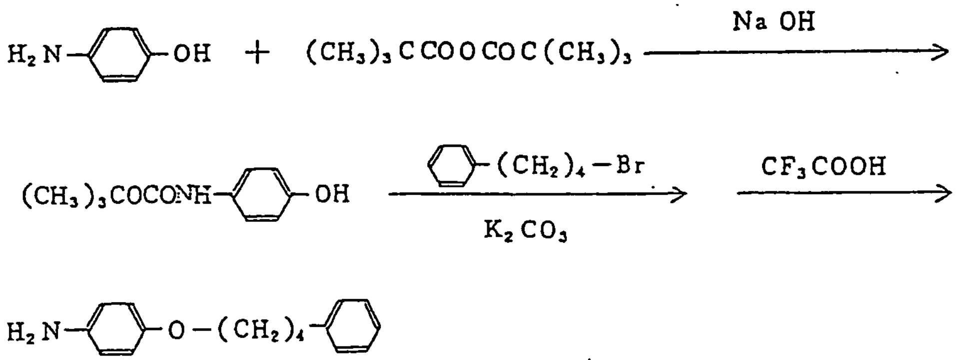
1-Ethoxycarbonylpiperazine and 1-bromo-3-phenylpropane were used as the starting materials and treated in the same manner as in Reference Example 9 to give 1-(3-phenylpropyl)piperazine.

NMR ($CDCl_3$)

δ: 1.63 ~ 1.97 (2H, m), 2.44 ~ 3.00 (12H, m), 7.04 ~ 7.44 (5H, m)

MS: m/z 203 (M^+)

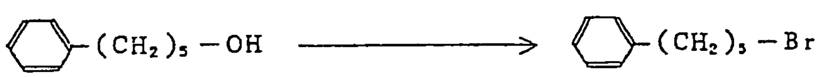
REFERENCE EXAMPLE 11



A solution of 6.43 g of di-tert-butyl dicarbonate in 5 ml of THF was added to a mixture of 3.06 g of p-aminophenol and 30 ml of 10% aqueous solution of sodium hydroxide at room temperature. The mixture was stirred at 80°C for 12 hours, then cooled and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography (eluent: hexane-ethyl acetate = 4:1) to give 4.35 g of p-(tert-butoxycarbonylamino)phenol. A mixture of 300 mg of the thus-obtained compound, 210 mg of potassium carbonate and 10 ml of 2-butanone was stirred at room temperature for 30 minutes, then a solution of 310 mg of 1-bromo-4-phenylbutane in 5 ml of 2-butanone was added, and the mixture was stirred at 80° C for 12 hours. After cooling, water was added to the reaction mixture, and the organic matter was extracted with ethyl acetate. The extract was washed in sequence with water and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate = 10:1) to give 1-(tert-butoxycarbonylamino)-4-(4-phenylbutoxy)benzene (0.2 g). Trifluoroacetic acid (5 ml) was added to the compound obtained with ice cooling, and the mixture was stirred with ice cooling for 30 minutes. The reaction mixture was concentrated under reduced pressure, washed with saturated aqueous solution of sodium hydrogen carbonate and then with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 0.13 g of p-(4-phenylbutoxy)aniline.

NMR ($CDCl_3$)
δ: 1.66~1.90 (4H, m), 2.67 (2H, t), 3.90 (2H, t), 6.56~6.82 (4H, m), 7.13~7.33 (5H, m)
MS: m/z 241 (M^+)

REFERENCE EXAMPLE 12



A mixture of 20 g of 5-phenylpentan-1-ol and 30 ml of 47% hydrobromic acid was refluxed for 6 hours. The reaction mixture was cooled and extracted with n-hexane. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: n-hexane-ethyl acetate = 100:1) to give 16.87 g of 1-bromo-5-phenylpentane.

NMR ($CDCl_3$)
δ: 1.28~2.03 (6H, m), 2.63 (2H, t), 3.42 (2H, t), 7.08~7.40 (5H, m)
MS: m/z 228 ($M^+ + 1$)

REFERENCE EXAMPLE 13

(1)

Methanesulfonyl chloride (1.52 g) was added dropwise to a solution of 1.11 g of cyclopentanemethanol and

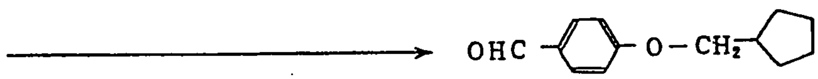
1.50 g of triethylamine in 30 ml of dichloromethane with cooling on an ice bath over 5 minutes. The reaction mixture was stirred at room temperature for 30 minutes and then washed in sequence with three portions of water and one portion of saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 2.06 g of cyclopentanemethyl methanesulfonate.

NMR ($CDCl_3$)

δ: 1.1~1.9 (8H), 2.1~2.5 (1H, m), 2.02 (3H, s), 4.13 (2H, d, J=7Hz),

MS: m/z 178 (M^+)

(2)



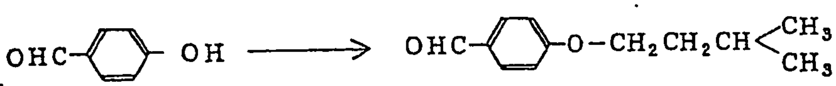
A mixture of 0.80 g of cyclopentanemethyl methanesulfonate obtained in (1), 0.60 g of p-hydroxybenzaldehyde and 0.93 g of anhydrous potassium carbonate in 6 ml of N,N-dimethylformamide was stirred overnight at 70° C. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with 1 N sodium hydroxide, water and saturated aqueous solution of sodium chloride in that order, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 460 mg of p-cyclopentanemethoxybenzaldehyde.

NMR ($CDCl_3$)

δ: 1.2~2.0 (8H), 2.40 (1H, quintet, J=7Hz), 3.92 (2H, d, J=7Hz), 6.99 (2H, d, J=10HZ), 7.86 (2H, d, J=10Hz), 9.88 (1H, s)

MS: m/z 204 (M^+)

REFERENCE EXAMPLE 14



A mixture of 1.00 g of p-hydroxybenzaldehyde, 1.46 g of isoamyl iodide and 1.80 g of potassium carbonate in 15 ml of N,N-dimethylformamide was stirred at room temperature for 2 days. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed in sequence with 1 N sodium hydroxide, water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 1.34 g of p-(3-methylbutoxy)benzaldehyde.

NMR ($CDCl_3$)

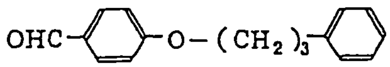
δ: 0.97 (6H, d, J=7Hz), 1.6~1.9 (3H), 4.08 (2H, t, J=7Hz), 6.99 (2H, d, J=8Hz), 7.87 (2H, d, J=8Hz), 9.90 (1H, s)

MS: m/z 192 (M^+)

REFERENCE EXAMPLES 150 TO 17

The following compounds were obtained in the same manner as in Reference Example 14.

Ref. Ex. 15



p-(3-Phenylpropoxy)benzaldehyde

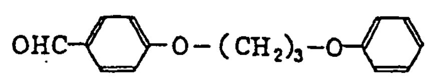
Physicochemical properties

NMR ($CDCl_3$)

δ: 2.18 (2H, m), 2.83 (2H, br t), 4.03 (2H, t, J=7Hz), 6.87 (2H, d, J=9Hz), 7.22 (5H, br), 7.82 (2H, d, J=9Hz), 9.88 (1H, s)

MS: m/z 240 (M^+)

Ref. Ex. 16



p-(3-Phenoxypropoxy)benzaldehyde

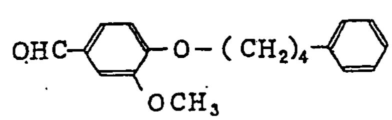
Physicochemical properties

NMR ($CDCl_3$)

δ: 2.30 (2H, quintet, J=6Hz), 4.19 (2H, t, J=6Hz), 4.39 (2H, t, J=6Hz), 6.7~7.3 (7H), 7.87 (2H, d, J=9Hz), 9.93 (1H, s)

MS: m/z 256 (M^+)

Ref. Ex. 17



3-Methoxy-4-(4-phenylbutoxy)benzaldehyde

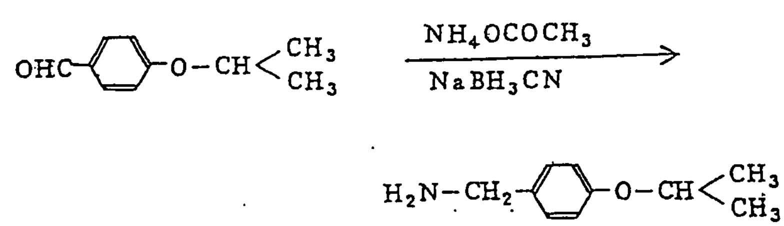
Physicochemical properties

NMR ($CDCl_3$)

δ: 1.6~2.0 (4H), 2.6~2.8 (2H), 3.90 (3H, s), 4.10 (2H, br, t), 6.93 (2H, d, J=9Hz), 7.1~7.5 (7H), 9.85 (1H, s)

MS: m/z 284 (M^+)

REFERENCE EXAMPLE 18



Sodium cyanoborohydride (330 mg) was added to a solution of 770 mg of p-isopropoxybenzaldehyde and 4.0 g of ammonium acetate in 20 ml of methanol, and the mixture was stirred at room temperature for 40 hours.

The reaction mixture was adjusted to pH 2 or less by addition of concentrated hydrochloric acid, and then concentrated. The residue was dissolved in water and the solution was washed with ethyl acetate. The aqueous layer was adjusted to pH 11 or more by addition of solid potassium hydroxide, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated aqueous solution of sodium chloride in that order, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 110 mg of p-isopropoxybenzylamine.

NMR ($CDCl_3$)

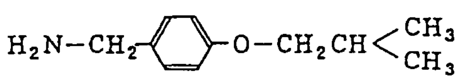
δ: 1.28 (6H, d, J=6Hz), 1.50 (2H, exchange with D_2O), 3.71 (2H, s), 4.46 (1H, hep., J=6Hz), 6.75 (2H, d, J=8Hz), 7.14 (2H, d, J=8Hz)

MS: m/z 165 (M^+)

REFERENCE EXAMPLES 19 TO 21

The following compounds were obtained in the same manner as in Reference Example 18.

Ref. Ex. 19



p-(2-Methylpropoxy)-benzylamine

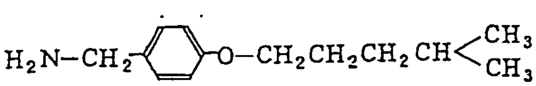
Physicochemical properties

NMR ($CDCl_3$)

δ: 1.02 (6H, d, J=7Hz), 1.5 (2H, exchange with D_2O), 2.06 (1H), 3.70 (2H, d, J=6Hz), 3.77 (2H, s), 6.84 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz)

MS: m/z 179 (M^+)

Ref. Ex. 20



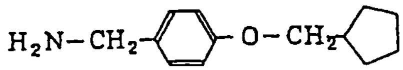
p-(4-Methylpentyloxy)-benzylamine

Physicochemical properties

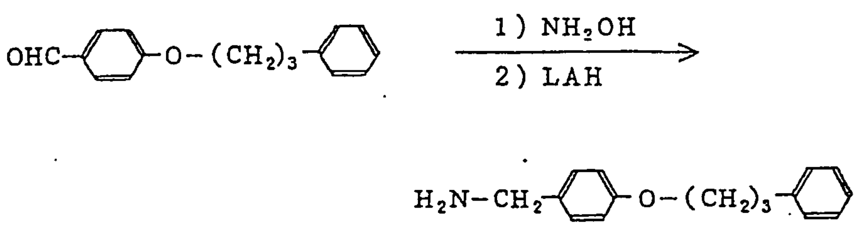
NMR ($CDCl_3$)

δ: 0.97 (6H, d, J=6Hz), 1.5 (2H, exchange with D_2O), 1.3~2.1 (5H), 3.78 (2H, s), 3.95 (2H, t, J=6Hz), 6.86 (2H, d, J=9Hz), 7.23 (2H, d, J=9Hz)

MS: m/z 207 (M^+)

Ref. Ex. 21	Physicochemical properties
 p-Cyclopentylmethoxybenzylamine	NMR ($CDCl_3$) δ: 1.2~1.9 (10H), 1.38 (1H, m), 3.80 (2H, s), 3.83 (2H, d, J=7Hz), 6.87 (2H, d, J=9Hz), 7.23 (2H, d, J=9Hz) MS: m/z 205 (M^+)

REFERENCE EXAMPLE 22



A solution of 750 mg of p-(3-phenylpropoxy)benzaldehyde and 2.3 g of hydroxylamine hydrochloride in 20 ml of methanol was adjusted to pH 8 by addition of 10% sodium hydroxide under cooling. The mixture was stirred for 1 hour and, then, the methanol was evaporated. water was added to the residue, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated to give 750 mg of p-(3-phenylpropoxy)benzaldehyde oxime. A solution of this compound in 10 ml of tetrahydrofuran was added dropwise to a suspension of 300 mg of lithium aluminum hydride in 6 ml of tetrahydrofuran at -30°C. After 20 minutes of stirring at -30°C, the temperature was raised to room temperature and stirring was continued for 2 hours. The excess lithium aluminum hydride was decomposed with sodium sulfate decahydrate, and the reaction mixture was filtered. The filtrate was diluted with ethyl acetate and washed with 10% hydrochloric acid. The hydrochloric acid layer was made alkaline with solid potassium hydroxide, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed in sequence with water and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 260 mg of p-(3-phenylpropoxy)benzylamine.

NMR ($CDCl_3$)

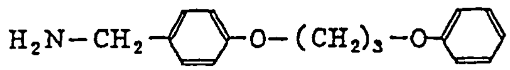
δ: 1.6 (2H, exchange with D_2O), 2.00~2.35 (2H, m), 2.70~3.00 (2H, m), 3.81 (2H, s), 3.97 (2H, t, J=6Hz), 6.87 (2H, d, J=9Hz), 7.24 (2H, d, J=9Hz), 7.25 (5H, s)

MS: m/z 241 (M^+)

REFERENCE EXAMPLES 23 TO 27

The following compounds were obtained in the same manner as in Reference Example 22.

Ref. Ex. 23



2-(3-Phenoxypropoxy)-
benzylamine

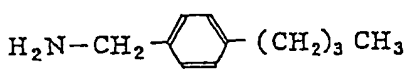
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.75 (2H, exchange with D_2O), 2.23 (2H, quintet, J=6Hz), 3.76 (2H, s), 4.14 (4H, t, J=6Hz), 6.8~7.4 (9H)

MS: m/z 257 (M^+)

Ref. Ex. 24



p-Butylbenzylamine

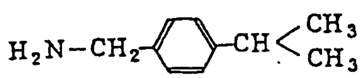
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.91 (3H, t, J=7Hz), 1.2~1.7 (4H), 1.6 (2H, exchange with D_2O), 2.60 (2H, t, J=7Hz), 3.82 (2H, s), 7.1~7.3 (4H)

MS: m/z 163 (M^+)

Ref. Ex. 25



p-Isopropylbenzylamine

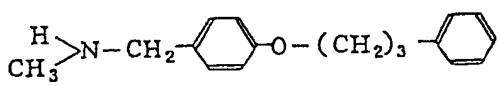
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.24 (6H, d, J=7Hz), 1.60 (2H, exachange with D_2O), 2.90 (1H, heptet, J=7Hz), 3.83 (2H, s), 7.23 (4H, br s)

MS: m/z 149 (M^+)

Ref. Ex. 26



N-Methyl-N-[p-(3-phenyl-propoxy)benzyl]amine

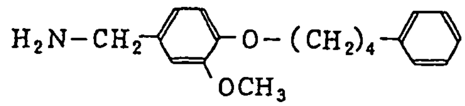
Physicochemical Properties

NMR ($CDCl_3$)

δ: 2.0~2.3 (2H), 2.2 (1H, exchange with D_2O), 2.43 (3H, s), 2.7~2.9 (2H), 3.69 (2H, s), 3.96 (2H, t, J=7Hz), 6.85 (2H, d, J=9Hz), 7.23 (2H, d, J=9Hz), 7.24 (5H)

MS: m/z 255 (M^+)

Ref. Ex. 27



[3-Methoxy-4-(4-phenylbutoxy)]benzylamine

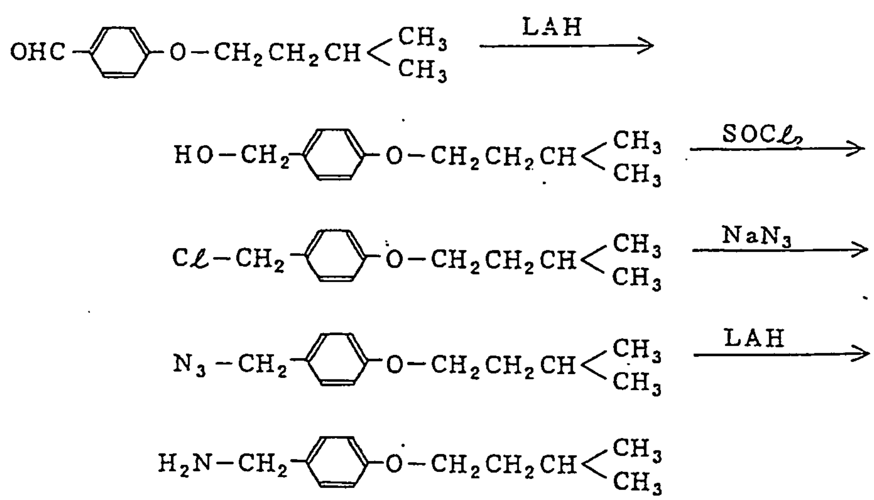
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.5~1.9 (6H), 2.7 (2H, m), 3.49 (2H, br s), 3.87 (3H, s), 4.0 (2H, m), 6.8~7.0 (3H), 7.2~7.3 (5H)

MS: m/z 285 (M^+)

REFERENCE EXAMPLE 28



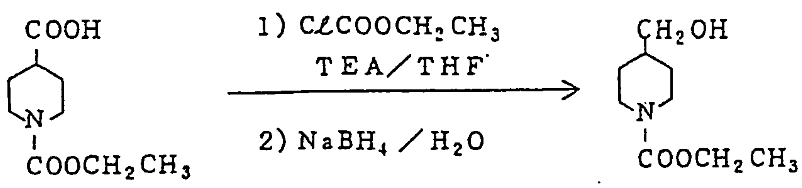
Lithium aluminum hydride (350 mg) was added gradually to a solution of 1.35 g of p-(3-methylbutoxy)benzaldehyde in 50 ml of tetrahydrofuran at -10°C. After stirring at room temperature for 1 hour, the excess lithium aluminum hydride was decomposed with sodium sulfate decahydrate. The insoluble matter was filtered off from the mixture, and the filtrate was concentrated to give 1.33 g of p-(3-methylbutoxy)benzyl alcohol. Thionyl chloride (3 g) was added to a solution of the compound obtained in 25 ml of benzene, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to give 1.45 g of p-(3-methylbutoxy)benzyl chloride. To a solution of this compound in 50 ml of N,N-dimethylformamide, there was added a solution of 3.3 g of sodium azide in 14 ml of water with ice cooling. After overnight stirring at room temperature, the reaction mixture was diluted with water, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 1.48 g of p-(3-methylbutoxy)benzyl azide. To a solution of this compound in 30 ml of tetrahydrofuran was added 500 mg of lithium aluminum hydride with ice cooling. The temperature of the reaction mixture was allowed to gradually rise to room temperature, and the mixture was stirred for 2 hours. The excess lithium aluminum hydride was decomposed with sodium sulfate decahydrate. The insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure to give 1.13 g of p-(3-methylbutoxy)benzylamine.

NMR ($CDCl_3$)

δ: 0.95 (6H, d, J=7Hz), 1.5 (2H, exchange with D_2O), 1.6~1.9 (3H), 3.80 (2H, s), 3.98 (2H, t, J=7Hz), 6.87 (2H, d, J=9HZ), 7.24 (2H, d, J=9Hz)

MS: m/z 193 (M^+)

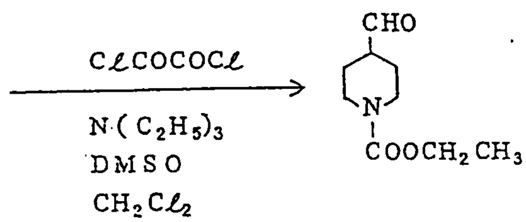
REFERENCE EXAMPLE 29



A solution of 0.67 g of ethyl chloroformate in 2 ml of tetrahydrofuran was added to a solution of 1.01 g of ethyl 4-carboxypiperidine-1-carboxylate and 0.72 g of triethylamine in 20 ml of tetrahydrofuran at -10 to -5° C, and the mixture was stirred for 30 minutes. The resultant crystalline precipitate was filtered off, the filtrate was added to a solution of 0.57 g of sodium borohydride in 10 ml of water with ice cooling over 30 minutes, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was made acidic with 1 N hydrochloric acid with ice cooling and then extracted with ether. The ether layer was washed in sequence with water, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. Elution with a hexane-ethyl acetate (1:1 v/v) mixture gave 0.69 g of ethyl 4-hydroxymethylpiperidine-1-carboxylate.

NMR ($CDCl_3$)
δ: 0.88 ~ 1.42 (1H, br), 1.30 (3H, t, J = 7.0Hz), 1.42 ~ 2.00 (5H, m), 2.77 (2H, dt, J = 12.0, 3.0Hz), 3.52 (2H, d, J = 6.0Hz), 4.15 (2H, q, J = 7.0Hz), 4.00 ~ 4.36 (2H, m)
MS: m/z 187 (M^+)

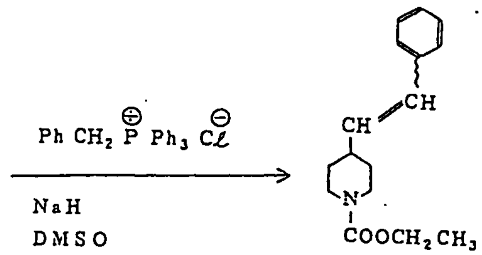
(2)



A solution of 1.97 g of dimethyl sulfoxide in 5 ml of dichloromethane was added to a solution of 1.59 g of oxalyl chloride in 30 ml of dichloromethane at a temperature within the range of -60 to -50° C. Five minutes layer, a solution of 2.11 g of ethyl 4-hydroxymethylpiperidine-1-carboxylate in 10 ml of dichloromethane was added dropwise, and the resultant mixture was stirred for 15 minutes. Triethylamine (5.73 g) was added to the reaction mixture, the whole mixture was stirred for 5 minutes and then at room temperature for 15 minutes. water was added to the reaction mixture, and the resultant mixture was extracted with dichloromethane. The organic layer was washed in sequence with 1 N hydrochloric acid and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 1.97 g of ethyl 4-formylpiperidine-1-carboxylate.

NMR ($CDCl_3$)
δ: 1.25 (3H, t, J = 7.0Hz), 1.42 ~ 2.10 (4H, m), 2.24 ~ 2.65 (1H, m), 2.65 ~ 3.24 (2H, m), 3.82 ~ 4.41 (4H, m), 9.68 (1H, s)
MS: m/z 185 (M^+)

(3)



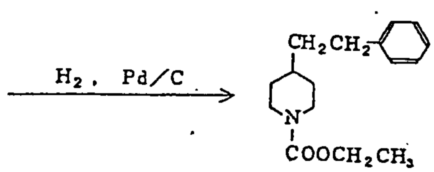
Sodium hydride (0.24 g) was added to 6 ml of dimethyl sulfoxide, the mixture was stirred at 75°C for 30 minutes and then cooled to room temperature. Thereto was added a suspension of 2.1 g of benzyltriphenylphosphonium chloride in 5 ml of dimethyl sulfoxide at room temperature, and the mixture was stirred for 15 minutes. To this mixture was added a solution of 0.93 g of ethyl 4-formylpiperidine-1-carboxylate in 5 ml of dimethyl sulfoxide, and the mixture was stirred for 1 hours. After addition of water, the mixture was extracted with ether, and the organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to purification by silica gel column chromatography (35 g). Elution with a hexane-ethyl acetate (3:1) mixture gave 1.13 g of ethyl 4-styrylpiperidine-1-carboxylate.

NMR ($CDCl_3$)

δ: 1.29 (3H, t, J=7.0Hz), 1.10~1.95 (4H, m), 2.03~2.58 (1H, m), 2.58~3.05 (2H, m), 4.16 (2H, q, J=7.0Hz), 3.88~4.40 (2H, m), 5.46 (1/7H, dd, J=12.0, 10.0Hz), 6.13 (6/7H, dd, J=16.0, 6.0Hz), 6.42 (1/7H, d, J=12.0Hz), 6.43 (6/7H, d, J=16.0Hz), 7.08~7.45 (5H, m)

MS: m/z 259 (M^+)

(4)



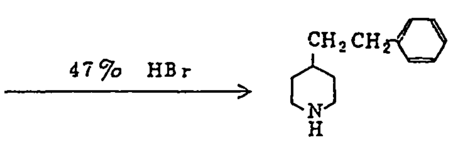
A mixture of 0.80 g of ethyl 4-styrylpiperidine-1-carboxylate and 80 mg of 10% palladium-on-carbon in ethyl acetate (40 ml) was subjected to catalytic reduction at room temperature until stopping of hydrogen absorption. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 0.80 g of ethyl 4-(2-phenylethyl)piperidine-1-carboxylate.

NMR ($CDCl_3$)

δ: 1.28 (3H, t, J=8.0Hz), 0.72~2.01 (7H, m), 2.50~2.98 (4H, m), 3.89~4.42 (2H, m), 4.14 (2H, q, J=8.0Hz), 7.02~7.54 (5H, m)

MS: m/z 261 (M^+)

(5)



A mixture of 0.70 g of ethyl 4-(2-phenylethyl)piperidine-1-carboxylate in 6 ml of 47% hydrobromic acid was heated under reflux at 100°C for 6 hours. A small amount of water was added for dissolution of the resultant crystals, the solution was washed with ether, and the aqueous layer was made alkaline with 20% sodium hydroxide. After salting out with sodium chloride, the aqueous layer was extracted with ether. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 0.42 g of 4-(2-phenylethyl)piperidine.

δ:0.78~2.06 (8H, m), 2.30~2.86 (4H, m), 2.86~3.32 (2H, m), 6.95~7.50 (5H, m)

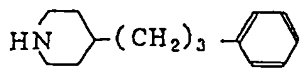
MS: m/z 189 (M^+)

REFERENCE EXAMPLES 30 TO 32

The ethyl 1-(4-formyl)piperidinecarboxylate of Reference Example 29 (2) and $Ph(CH_2)_uP^{\oplus}Ph \cdot Br^{\oplus}$ (u=2 to 4) were used and treated in the same manner as in Reference Example 29 (3) to (5) to give the following

compounds:

Ref. Ex. 30



4-(3-Phenylpropyl)-piperidine

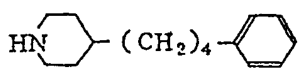
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.75~2.05 (10H, m),
2.30~2.76 (4H, m),
2.83~3.24 (2H, m),
7.04~7.49 (5H, m)

MS: m/z 203 (M^+)

Ref. Ex. 31



4-(4-Phenylbutyl)-piperidine

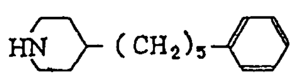
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.78~1.82 (11H, m),
1.12 (1H, s),
2.35~2.75 (4H, m),
2.84~3.21 (2H, m),
7.04~7.45 (5H, m)

MS: m/z 217 (M^+)

Ref. Ex. 32



4-(5-Phenylpentyl)-piperidine

Physicochemical Properties

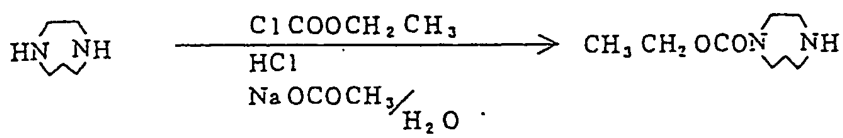
NMR ($CDCl_3$)

δ: 0.81~1.90 (14H, m),
2.35~2.80 (4H, m),
2.86~3.23 (2H, m),
7.02~7.42 (5H, m)

MS: m/z 231 (M^+)

REFERENCE EXAMPLE 33

(1)



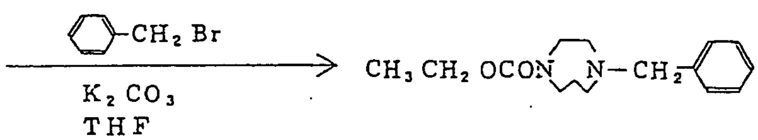
2 N Hydrochloric acid was added to a solution of 1.10 g of homopiperazine in 15 ml of water at room temperature until a pH of 2 was attained. Then, 40% aqueous sodium acetate and 1.28 g of ethyl chloroformate were added alternately in portions within the pH range of 2.0 to 3.5, and the resultant mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with ethyl acetate, and the aqueous layer was saturated with potassium carbonate and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 1.27 g of ethyl 1-homopiperazinecarboxylate.

NMR ($CDCl_3$)

δ: 1.28 (3H, t, J=7Hz), 1.60~1.99 (3H, m), 2.75~3.04 (4H, m), 3.30~3.65 (4H, m), 4.15 (2H, q, J=7Hz)

MS: m/z 172 (M^+)

(2)



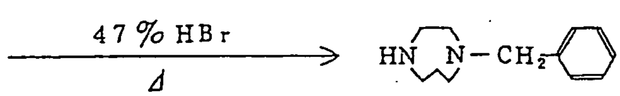
Potassium carbonate (0.80 g) was added to a solution of 0.86 g of ethyl 1-homopiperazinecarboxylate and 0.90 g of benzylbromide in 5 ml of tetrahydrofuran, and the mixture was refluxed for 4 hours. Thereafter, water was added, and the mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. Elution with a hexane-ethyl acetate (2:1) mixture gave 1.06 g of ethyl 4-benzylhomopiperazine-1-carboxylate.

NMR ($CDCl_3$)

δ: 1.25 (3H, t, J=7Hz), 1.62~2.05 (2H, m), 2.50~2.81 (4H, m), 3.32~3.75 (4H, m), 3.61 (2H, s), 4.14 (2H, q, J=7Hz), 7.29 (5H, s)

MS: m/z 262 (M^+)

(3)



A mixture of 0.85 g of ethyl 4-benzylhomopiperazine-1-carboxylate and 5 ml of 47% hydrobromic acid was heated at 100°C for 10 hours. After addition of a small amount of water, the reaction mixture was washed with ethyl acetate. The aqueous layer was made alkaline with 30% sodium hydroxide and, after salting out with sodium chloride, extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 0.55 g of 1-benzylhomopiperazine.

NMR ($CDCl_3$)

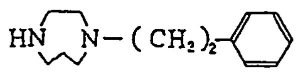
δ: 1.60~1.96 (2H, m), 1.91 (1H, s), 2.52~2.80 (4H, m), 2.80~3.07 (4H, m), 3.68 (2H, s), 7.12~7.45 (5H, m)

MS: m/z 190

REFERENCE EXAMPLES 34 TO 37

The following compounds were obtained in the same manner as in Reference Example 33 (2) and (3).

Ref. Ex. 34



1-(2-Phenylethyl)homopiperazine

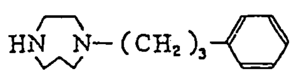
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.60~1.92 (2H, m),
2.03 (1H, s),
2.58~3.09 (12H, m),
7.05~7.43 (5H, m)

MS: m/z 204 (M^+)

Ref. Ex. 35



1-(3-Phenylpropyl)homopiperazine

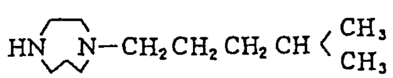
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.58~1.98 (4H, m),
2.08 (1H, s),
2.16~2.78 (8H, m),
2.78~3.02 (4H, m),
6.95~7.45 (5H, m)

MS: m/z 218 (M^+)

Ref. Ex. 36



1-(4-Methylpentyl)homopiperazine

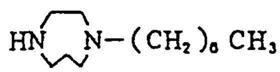
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.89 (6H, d, J=6Hz),
0.96~2.91 (7H, m),
2.11 (1H, s),
2.35~2.57 (2H, m),
2.57~2.79 (4H, m),
2.80~3.04 (4H, m)

MS: m/z 184 (M^+)

Ref. Ex. 37



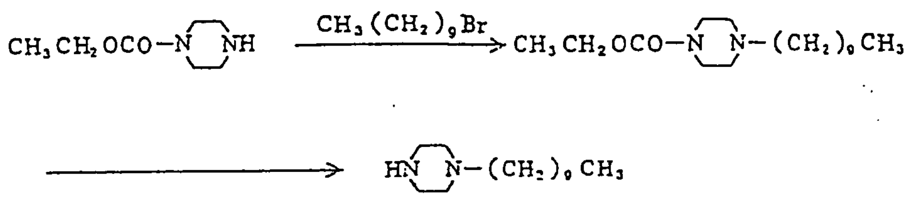
1-Heptylhomopiperazine

Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.73~1.01 (3H, m),
1.08~1.61 (11H, m),
1.63~1.93 (2H, m),
2.32~2.80 (6H, m),
2.82~3.08 (4H, m).

REFERENCE EXAMPLE 38



A mixture of 2.02 g of ethyl 1piperazinecarboxylate, 1.92 g of anhydrous potassium carbonate, 3.08 g of decyl bromide and 20 ml of 2-butanone was stirred overnight at 80° C. After addition of water, the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was extracted with 3 N hydrochloric acid. The extract was made alkaline with potassium carbonate and then extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Ethanol (20 ml) and 20 ml of 10% aqueous sodium hydroxide were added to the residue, and the mixture was stirred overnight at 100° C. The reaction mixture was cooled and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 0.38 g of 1-decylpiperazine as an oil.

NMR ($CDCl_3$)

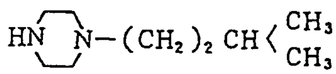
δ: 0.73~1.74 (19H, m), 2.16~2.52 (6H, m), 2.84~2.98 (4H, m)

MS: m/z 226 (M^+)

REFERENCE EXAMPLES 39 TO 50

The following compounds were obtained in the same manner as in Reference Example 38.

Ref. Ex. 39



1-(3-Methylbutyl)-
piperazine

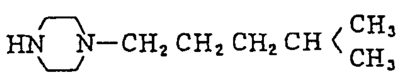
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.89 (6H, d),
1.12~1.74 (3H, m),
2.13~2.52 (6H, m),
2.80~3.00 (4H, m)

MS: m/z 156 (M^+)

Ref. Ex. 40



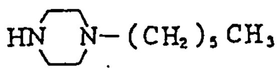
1-(4-Methylpentyl)-
piperazine

Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.88 (6H, d, J=7Hz),
1.00~1.73 (5H, m),
2.09 (1H, s),
2.17~2.56 (4H, m),
2.78~3.05 (4H, m)

Ref. Ex. 41



1-Hexylpiperazine

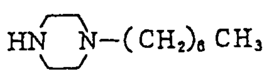
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.90 (3H, t),
1.12~1.72 (8H, m),
2.20~2.52 (6H, m),
2.82~3.00 (4H, m)

MS: m/z 170 (M^+)

Ref. Ex. 42



1-Heptylpiperazine

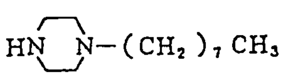
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.90 (3H, t),
1.14~1.72 (10H, m),
2.20~2.56 (6H, m),
2.80~3.04 (4H, m)

MS: m/z 184 (M^+)

Ref. Ex. 43



1-Octylpiperazine

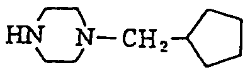
Physicochemical Properties

NMR ($CDCl_3$)

δ: 0.90 (6H, d),
1.12~1.40 (12H, m),
2.16~2.56 (6H, m),
2.80~3.00 (4H, m)

MS: m/z 178 (M^+)

Ref. Ex. 44



1-Cyclopentylmethyl-
piperazine

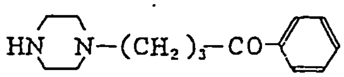
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.04~2.52 (15H, m),

2.80~3.00 (4H, m)

Ref. Ex. 45



1-(4-Oxo-4-phenylbutyl)-
piperazine

Physicochemical Properties

NMR ($CDCl_3$)

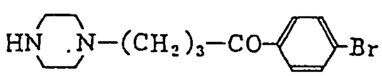
δ: 1.72~3.20 (14H, m),

7.26~7.64 (3H, m),

7.90~8.10 (2H, m)

MS: m/z 231 (M^+)

Ref. Ex. 46



1-[4-(p-Bromophenyl)-4-
oxobutyl]piperazine

Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.80~2.10 (4H, m),

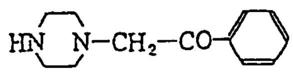
2.26~2.50 (6H, m),

2.72~2.90 (4H, m),

7.52~7.72 (2H, m),

7.76~8.00 (2H, m)

Ref. Ex. 47



1-(2-Oxo-2-phenylethyl)-piperazine

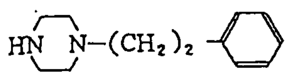
Physicochemical Properties

NMR ($CDCl_3$)

δ: 2.40~2.76 (4H, m),
2.76~3.12 (4H, m),
3.80 (2H, s),
7.22~7.64 (3H, m),
7.88~8.14 (2H, m)

MS: m/z 204 (M^+)

Ref. Ex. 48



1-(2-Phenylethyl)-piperazine

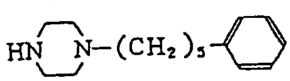
Physicochemical Properties

NMR ($CDCl_3$)

δ: 2.23~2.97 (12H, m),
7.10~7.36 (5H, m)

MS: m/z 189 (M^+)

Ref. Ex. 49



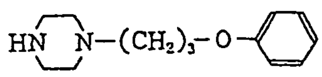
1-(5-Phenylpentyl)-piperazine

Physicochemical Properties

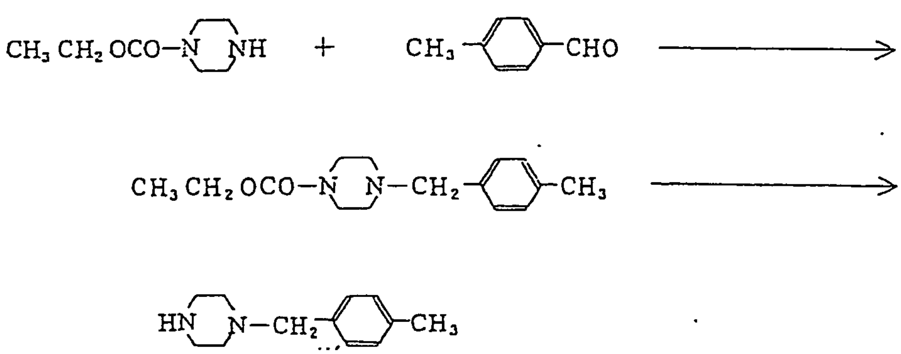
NMR ($CDCl_3$)

δ: 1.14~1.84 (6H, m),
2.16~2.72 (8H, m),
2.78~3.02 (4H, m),
7.04~7.40 (5H, m)

MS: m/z 231 (M^+)

Ref. Ex. 50	Physicochemical Properties
 1-(3-Phenoxypropyl)-piperazine	NMR ($CDCl_3$) δ: 1.6~2.3 (2H, m), 2.4~3.2 (10H, m), 4.06 (2H, t), 6.7~7.5 (5H, m)

REFERENCE EXAMPLE 51

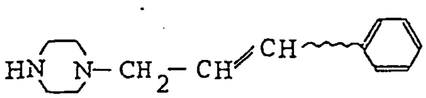


Sodium borohydride (500 mg) was added to a mixture of 1.6 g of ethyl 1-piperazinecarboxylate, 1.3 g of p-tolualdehyde and 30 ml of ethanol, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, 50 ml of water was added, and the resultant mixture was extracted with ethyl acetate. The ethyl acetate extract was then extracted with diluted hydrochloric acid. The diluted hydrochloric acid extract was washed with ethyl acetate, made alkaline with sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous potassium carbonate and concentrated under reduced pressure to give 0.8 g of ethyl 4-p-tolylmethyl-1-piperazinecarboxylate as an oil. This was deprived of the carboethoxy group by the method described in Reference Example 38 to give 0.36 g of 1-p-tolylmethylpiperazine as an oil.

NMR ($CDCl_3$)

δ: 2.42 (3H, s, CH_3), 2.3~2.6 (4H, m), 2.7~3.1 (4H, m), 3.43 (2H, s, CH_2), 7.14 (4H, s)

REFERENCE EXAMPLE 52

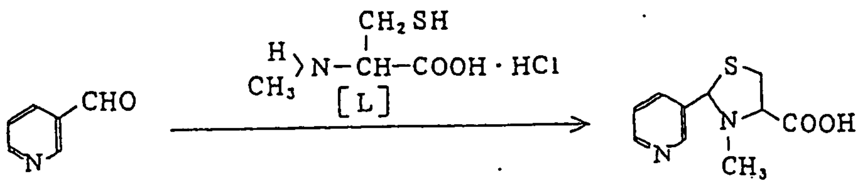


Ethyl 1-piperazinecarboxylate and cinnamaldehyde were used as the starting materials and treated in the same manner as in Reference Example 51 to give 1-cinnamylpiperazine as an oil.

NMR ($CDCl_3$)

δ: 2.2~2.6 (4H, m), 2.8~3.0 (4H, m), 3.16 (2H, d, CH_2), 6.28 (1H, dt), 6.56 (1H, d), 7.0~7.5 (5H, m)

REFERENCE EXAMPLE 53



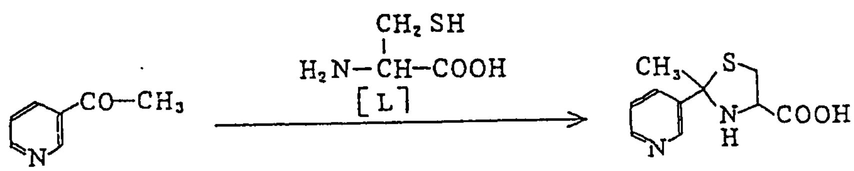
A mixture of 1.72 g of L-N-methylcysteine, 1.07 g of nicotinaldehyde and 2 ml of water was stirred at room temperature for 24 hours. pyridine (0.8 ml) and 1 ml of ethanol were added to the reaction mixture, and the resultant crystalline precipitate was collected by filtration, washed with ethanol and dried to give 0.74 g of 3-methyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid.

NMR (DMSO-d_6)

δ: 2.24, 2.32 ($^{3H}/_{2}\times 2$, s, N-CH_3), 3.00~3.64 ($^{5}/_{2}$H, m), 4.16~4.32 ($^{H}/_{2}$, m), 4.92, 5.36 ($^{h}/_{2}$, s), 7.10~7.32 (1H, m), 7.80~8.00 (1H, m), 8.44~8.72 (2H, m)

MS (FAB): m/z 225 $(M+H)^+$

REFERENCE EXAMPLE 54



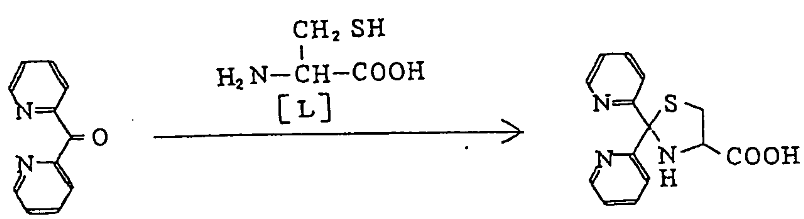
A mixture of 3.63 g of 3-acetylpyridine, 3.63 g of L-cysteine, 25 ml of water and 25 ml of ethanol was refluxed for 24 hours. The .reaction mixture was concentrated under reduced pressure, isopropanol was added to the residue, and the resultant powder was collected by filtration. Ethanol was added to the powder, the insoluble matter was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in water and adjusted to pH 6 by addition of diluted hydrochloric acid under ice colling and stirring, and the resultant powder was collected by filtration, washed with ethanol and dried to give 2.54 g of 2-methyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid.

NMR (DMSO-d_6)

δ: 1.78 and 1.88 (s, respectively 3H), 2.92~3.56 (2H, m), 3.56~4.38 (1H, m), 7.20~7.44 (1H, m), 7.80~9.08 (1H, m), 9.32~9.52 (1H, m), 9.68~9.86 (1H, m)

MS (FAB): m/z 225 $(M+H)^+$

REFERENCE EXAMPLE 55

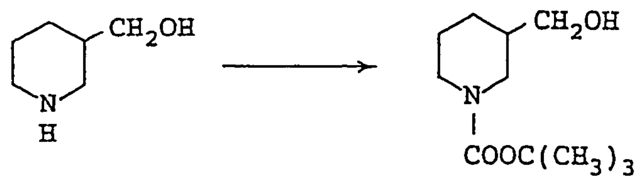


A mixture of 3.68 g of di-2-pyridyl ketone, 2.42 g of L-cysteine, 25 ml of water and 25 ml of ethanol was refluxed for 3.5 hours. After allowing the mixture to cool, the insoluble matter was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue was washed in sequence with ethyl acetate and ether to give 0.63 g of 2,2-di(2-pyridyl)thiazolidine-4-carboxylic acid.

NMR (DMSO-d_6)

δ: 2.85~4.15 (3H, m), 7.20~8.90 (8H, m)

REFERENCE EXAMPLE 56



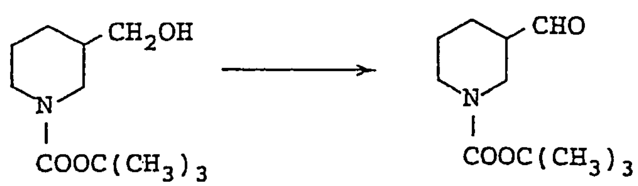
Di-tert-butyl dicarbonate (7.85 g) and 35 ml of 1 N sodium hydroxide were added to a solution of 4.00 g of 3-piperidinemethanol in 50 ml of dioxane plus 30 ml of water at 0° C. The reaction mixture was allowed to rise to room temperature and then stirred for 1.5 hours. The product was extracted with ethyl acetate. The ethyl acetate layer was washed in sequence with water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 7.20 g of 1-tert-butoxycarbonylpiperidine-3-methanol. Melting point 77-79° C.

NMR ($CDCl_3$)

δ: 1.48 (9H, s), 1.4~1.9 (4H), 2.6~3.2 (4H), 3.6~3.9 (4H)

MS: m/z 215 (M^+)

REFERENCE EXAMPLE 57



Dimethyl sulfoxide (0.85 ml) was added to a solution of 0.50 ml of oxalyl chloride in 10 ml of dichloromethane at -60°C and, 3 minutes later, a solution of 1.08 g of 1-tert-butoxycarbonylpiperidine-3-methanol in 10 ml of dichloromethane was added dropwise over 5 minutes. After stirring for 15 minutes, 3.0 ml of triethylamine was added to the reaction mixture. After further 5 minutes of stirring, water (20 ml) was added to the reaction mixture and, after shaking, the dichloromethane layer was separated. The dichloromethane layer was washed with 1 N hydrochloric acid, water, saturated aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride in that order, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 0.98 g of 1-tert-butoxycarbonylpiperidine-3-carbaldehyde.

NMR ($CDCl_3$)

δ: 1.46 (9H, s), 1.4~2.0 (4H), 2.40 (1H, m, w/z=21Hz), 3.10 (1H, dd, J=8.5 and 14Hz), 3.65 (1H, ddd, J=4, 5 and 12.5Hz), 3.94 (1H, dd, J=4 and 14Hz), 9.68 (1H, s)

MS: m/z 213 (M^+)

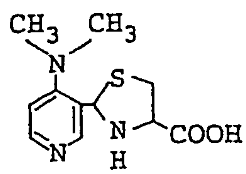
REFERENCE EXAMPLES 58 TO 67

The following compounds were obtained in the same manner as in Reference Example 2.

Desired Product

Chemical Structure and Chemical Name

Ref. Ex. 58



2-[3-(4-Dimethylamino-pyridyl)]thiazolidine-4-carboxylic acid

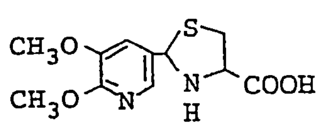
Physicochemical Properties

NMR (DMSO-d_6)

δ: 2.85 (6H, s), 2.98~3.56 (2H, m), 3.72~4.44 (1H, m), 5.68, 5.92 (1H, s), 6.80~7.00 (1H, m), 8.16~ 8.34 (1H, m), 8.60~8.75 (1H, m)

MS (FAB): m/z 254 $(M+H)^+$

Ref. Ex. 59



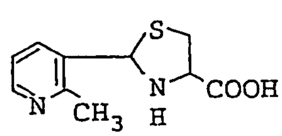
2-[3-(5,6-Dimethoxy-pyridyl)]thiazolidine-4-carboxylic acid

Physicochemical Properties

Melting point: 154~155°C (decomposition)

MS (FAB): m/z 271 $(M+H)^+$

Ref. Ex. 60



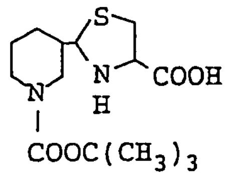
2-[3-(2-Methylpyridyl)]-thiazolidine-4-carboxylic acid

Physicochemical Properties

NMR (DMSO-d_6)

δ: 2.60 (3H, s), 2.80~4.60 (3H, m), 5.70, 6.00 (1H, s), 7.00~8.50 (3H, m)

Ref. Ex. 61



2-(1-tert-Butoxycarbonyl-4-piperidinyl)thiazolidine-4-carboxylic acid

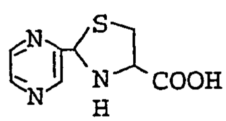
Physicochemical Properties

Melting point: 169~171°C (decomposition)

NMR ($CDCl_3$+DMSO-d_6)

δ: 1.48 (9H, s), 1.4~2.1 (5H), 2.6~3.0 (1H), 2.95 (1H, dd, J=7 and 10Hz), 3.22 (1H, dd, J=7 and 10Hz), 3.6~4.0 (1H), 3.96 (1H, t, J=7Hz), 4.49 (1H, d, J=8Hz), 6.3 (2H, br, exchange with D_2O)

Ref. Ex. 62



2-(2-Pyrazyl)thiazolidine-4-carboxylic acid

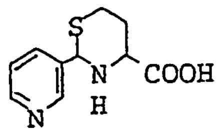
Physicochemical Properties

Melting point: 144~146°C (decomposition)

Elemental analysis (for $C_8H_9N_3O_2S$):

	C(%)	H(%)	N(%)	S(%)
Calcd:	45.49	4.29	19.89	15.18
Found:	45.20	4.18	19.76	15.43

Ref. Ex. 63



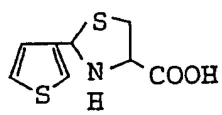
2-(3-Pyridyl)-3,4,5,6-tetrahydro-2H-thiazine-4-carboxylic acid

Physicochemical Properties

Melting point: 204~207°C

MS: m/z 225 (M^{+}+1)

Ref. Ex. 64



2-(3-Thienyl)thiazolidine-4-carboxylic acid

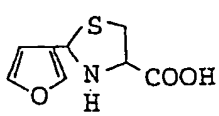
Physicochemical Properties

Melting point: 165~167°C

Elemental analysis (for $C_8H_9NO_2S_2$):

	C(%)	H(%)	N(%)	S(%)
Calcd:	44.63	4.21	6.51	29.79
Found:	44.57	4.23	6.49	29.99

Ref. Ex. 65



2-(3-Furyl)thiazolidine-4-carboxylic acid

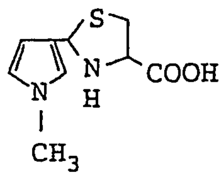
Physicochemical Properties

Melting point: 169~170°C (decomposition)

Elemental analysis (for $C_8H_9NO_3S$):

	C(%)	H(%)	N(%)	S(%)
Calcd:	48.23	4.55	7.03	16.09
Found:	48.03	4.51	7.00	16.28

Ref. Ex. 66



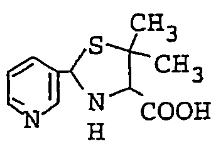
2-[3-(1-Methylpyrrolyl)]-thiazolidine-4-carboxylic acid

Physicochemical Properties

Melting point: 148~147°C (decomposition)

MS (FAB): m/z 213 (M^{+}+1)

Ref. Ex. 67



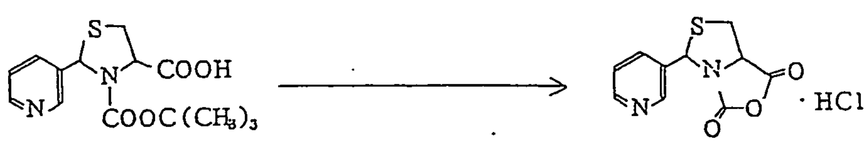
5,5-Dimethyl-2-(3-pyridyl)-thiazolidine-4-carboxylic acid

Physicochemical Properties

Melting point: 143~144°C

MS (FAB): m/z 1239 (M^{+}+1)

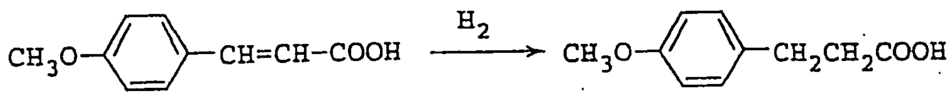
REFERENCE EXAMPLE 68



Oxalyl chloride (1.31 ml) and 50 mg of N,N-dimethylfornamide were added to a solution of 3.10 g of 3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid in 30 ml of dichloromethane at -78°C. The reaction mixture was slowly warmed to room temperature and then stirred for 12 hours. The resultant precipitate was collected by filtration and dried to give 1.90 g of 1,3-dioxo-5-(3-pyridyl)thiazolidino[3,4-c]oxazolidine.hydrochloride. Melting point 170°C (decomposition).
Elemental analysis (for $C_{10}H_9ClN_3O_3S$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	44.04	3.33	10.27	11.76	13.00
Found:	43.94	3.37	10.24	11.76	13.30

REFERENCE EXAMPLE 69

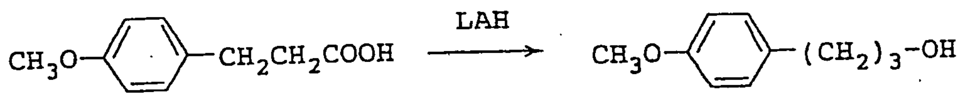


10% Palladium-on-carbon (200 mg) was added to a solution of 5.34 g of 4-methoxycinnamic acid in methanol, and the mixture was stirred under hydrogen until hydrogen gas absorption ceased. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give 5.43 g of 3-(4-methoxyphenyl)propionic acid.

NMR ($CDCl_3$)

δ: 2.34~3.15 (4H), 3.76 (3H, s), 6.64~7.30 (4H), 11.00 (1H, s)

REFERENCE EXAMPLE 70



A solution of the 3-(4-methoxyphenyl)propionic acid in 100 ml of anhydrous ether was added dropwise to a suspension of 1.10 g of lithium aluminum hydride in 50 ml of anhydrous ether with stirring at room temperature over 20 minutes. After stirring at room temperature for 30 minutes, the mixture was refluxed for 1 hours. After cooling, water was added with ice cooling, and the mixture was made acidic by further addition of 10% hydrochloric acid and then extracted with ether. The organic layer was washed with saturated aqueous solution of sodium chloride, driven over anhydrous magnesium sulfate and concentrated under reduced pressure to give 5.06 g of 3-(4-methoxyphenyl)propanol.

NMR ($CDCl_3$)

δ: 1.60~2.16 (2H), 2.38~2.95 (3H), 3.69 (2H, t, J=6Hz), 3.80 (3H, s), 6.71~7.30 (4H)

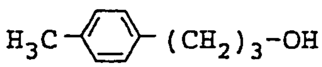
REFERENCE EXAMPLES 71 TO 74

The following compounds were obtained in the same manner as in Reference Examples 69 and 70. In Reference Examples 73 and 74, platinum oxide was used as a catalyst for the catalytic reduction.

Desired Compound

Chemical Structure and Chemical Name

Ref. Ex. 71



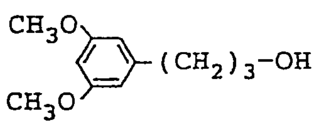
3-(4-Methylphenyl)propanol

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.58~2.10 (2H), 2.26 (3H, s), 2.49~2.83 (3H), 3.60 (2H, t, J=6Hz), 7.00 (4H, s)

Ref. Ex. 72



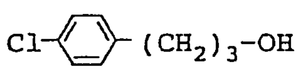
3-(3,4-Dimethoxyphenyl)-propanol

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.60~2.14 (2H), 2.49~2.90 (3H), 3.65 (2H, t), 3.82 (6H, s), 6.73 (3H, s)

Ref. Ex. 73



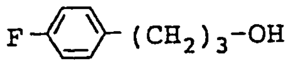
3-(4-Chlorophenyl)propan-ol

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.60~2.14 (2H), 1.77 (1H, s), 2.54~2.90 (2H), 3.65 (2H, t), 6.95~7.40 (4H)

Ref. Ex. 74



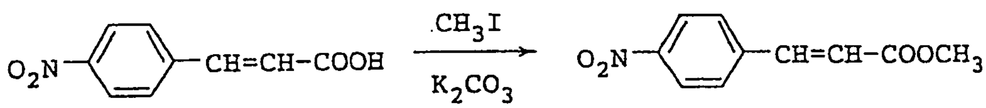
3-(4-Fluorophenyl)propan-ol

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.55~2.16 (2H), 2.01 (1H, s), 2.48~2.88 (2H), 3.65 (2H, t), 6.65~7.31 (4H)

REFERENCE EXAMPLE 75

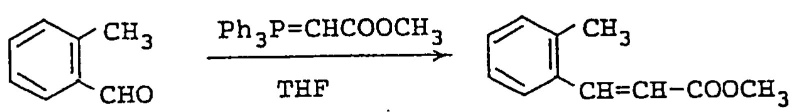


A mixture of 5.80 g of p-nitrocinnamic acid, 10.4 g of methyl iodide, 10.4 g of anhydrous potassium carbonate and 200 ml of acetone was stirred at room temperature for 2 days. The resultant precipitate was filtered off, the filtrate was concentrated under reduced pressure and, after addition of water, the residue was extracted with ethyl acetate. The organic layer was washed with saturated solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 3.30 g of methyl 4-nitrocinnamate.

NMR ($CDCl_3$)

δ: 3.83 (3H, s), 6.52 (1H, d, J=16Hz), 7.50~7.95 (3H), 8.21 (2H, d, J=9Hz).

REFERENCE EXAMPLE 76



A solution of 1.20 g of o-tolualdehyde in 20 ml of anhydrous tetrahydrofuran was added to a suspension of 3.67 g of methyl (triphenylphosphoranylidene)acetate in 20 ml of anhydrous tetrahydrofuran at room temperature, and the mixture was refluxed for 15 hours. The solvent was then distilled off under reduced pressure, and the residue was subjected to silica gel column chromatography (40 g). Elution with hexane-ethyl acetate (2:1) gave 1.65 g of methyl 2-methylcinnamate.

NMR ($CDCl_3$)

δ: trans-form, 2.45 (3H, s), 3.80 (3H, s), 6.34 (1H, d, J=16Hz), 6.99~7.66 (4H), 7.97 (1H, d, J=16Hz)
cis-form, 2.29 (s), 3.63 (s), 6.03 (d, J=12Hz)

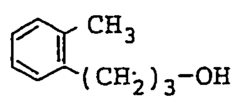
REFERENCE EXAMPLES 77 TO 78

The following compounds were synthesized in the same manner as in Reference Examples 69 and 70.

Desired Compound

Chemical Structure and Chemical Name

Ref. Ex. 77



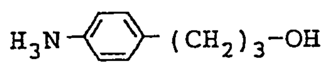
3-(2-Methylphenol)propanol

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.57~2.11 (2H), 1.86 (1H, s), 2.51~2.90 (2H), 3.69 (2H, t, J=6Hz), 7.10 (4H, s).

Ref. Ex. 78



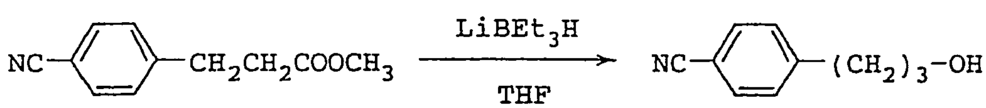
3-(4-Aminophenol)propanol

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.54~2.10 (2H), 2.40~3.10 (5H), 3.62 (2H, t, J=6Hz), 6.46~7.10 (4H).

REFERENCE EXAMPLE 79

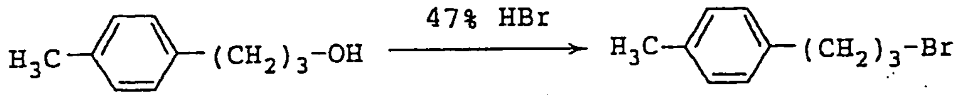


A solution of 1 M superhydride/tetrahydrofuran (3.3 ml) in anhydrous tetrahydrofuran (5 ml) was cooled to -50 to -60°C under an argon gas stream. Thereto was added dropwise a solution of 210 mg of methyl 3-(4-cyanophenyl)propionate synthesized from 4-cyanobenzaldehyde and methyl (triphenylphosphoranylidene)acetate by the procedure of Reference Examples 69 and 76) in 2 ml of tetrahydrofuran. The resultant mixture was stirred at that temperature for 10 minutes, then made acidic by addition of water and 1 N hydrochloric acid in that order at the same temperature, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 120 mg of 3-(4-cyanophenyl)propanol.

NMR ($CDCl_3$)

δ: 1.61~2.20 (3H), 2.60~3.06 (2H), 3.68 (2H, t, J=6Hz), 7.10~7.75 (4H)

REFERENCE EXAMPLE 80

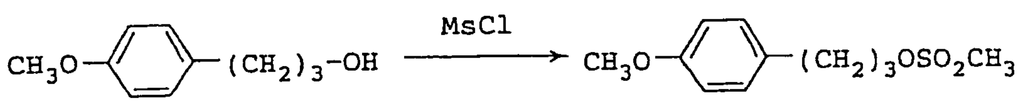


3-(4-Methylphenyl)propanol (2.13 g) was heated in 7 ml of 47% aqueous hydrobromic acid under reflux for 5 hours. The solvent was then distilled off under reduced pressure and, after addition of water, the residue was extracted with ether. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was distilled under reduced pressure to give 1.75 g of 3-(4-methylphenyl)propyl bromide. Boiling point: 65°C/0.7 mmHg.

NMR ($CDCl_3$)

δ: 1.85~2.43 (2H), 2.32 (3H, s), 2.55~2.95 (2H), 3.39 (2H, t, J=6Hz), 7.04 (4H, s)

REFERENCE EXAMPLE 81

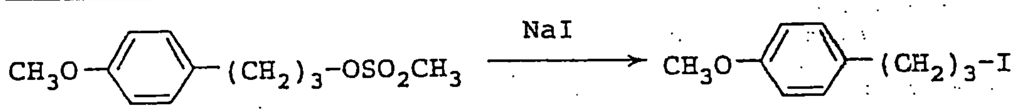


Methanesulfonyl chloride (3.8 g) was gradually added dropwise to a solution of 5 g of 3-(4-methoxyphenyl)propanol in 50 ml of anhydrous pyridine with ice cooling, and the resultant mixture was stirred at the same temperature for 3 hours. The solvent was distilled off under reduced pressure and, after addition of water, the residue was made acidic with 10% hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride in that order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6.32 g of 3-(4-methoxyphenyl)propylmethanesulfonate.

NMR ($CDCl_3$)

δ: 1.75~2.36 (2H), 2.55~2.93 (2H), 3.00 (3H, s), 3.80 (3H, s), 4.24 (2H, t, J=6Hz), 6.70~7.30 (4H).

REFERENCE EXAMPLE 82



A solution of 6.30 g of 3-(4-methoxyphenyl)propyl methanesulfonate and 11.1 g of sodium iodide in 100 ml of acetone was refluxed for 15 hours. The reaction mixture was concentrated under reduced pressure and, after addition of water, the residue was extracted with ether. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 6.62 g of 3-(4-methoxyphenyl)propyl iodide.

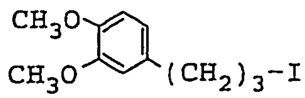
NMR ($CDCl_3$)

δ: 1.81~2.35 (2H), 2.18 (2H, br t, J=7Hz), 3.16 (2H, t, J=6Hz), 3.80 (3H, s), 6.71~7.30 (4H).

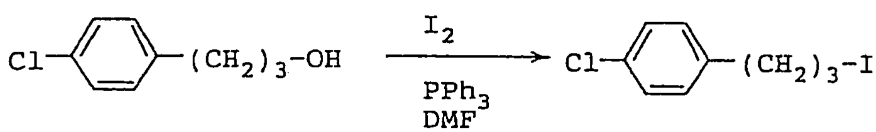
REFERENCE EXAMPLE 83

The following compound was obtained in the same manner as in Reference Example 82.

Desired Compound

Chemical Structure and Chemical Name	Physicochemical Properties
Ref. Ex. 83  3-(3,4-Dimethoxyphenyl)-propyl iodide	MMR ($CDCl_3$) δ: 1.80~2.34 (2H), 2.66 (2H, br t, J=7Hz), 3.12 (2H, t, J=6Hz), 3.81 (6H, s), 6.59 (3H, s).

REFERENCE EXAMPLE 84



To a solution of 1.55 g of 3-(4-chlorophenyl)propanol and 2.51 g of triphenylphosphine in 10 ml of N,N-dimethylformamide, there was gradually added dropwise at room temperature a solution of 2.42 g of iodine in 8 ml of N,N-dimethylformamide while confirming the consumption of iodine. When the color of the reaction mixture ceased to disappear any more, water was added to the reaction mixture, the excess iodine was reduced by addition of 5% aqueous sodium thiosulfate, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (20 g). Elution with hexane gave 1.82 g of 3-(4-chlorophenyl)propyl iodide.

NMR ($CDCl_3$)

δ: 1.92~2.40 (2H), 2.71 (2H, br t, J=7Hz), 3.13 (2H, t, J=6Hz), 6.91~7.40 (4H).

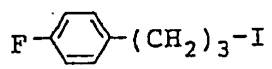
REFERENCE EXAMPLES 85 TO 87

The following compounds were obtained in the same manner as in Reference Example 84.

Desired Compound

Chemical Structure and Chemical Name

Ref. Ex. 85



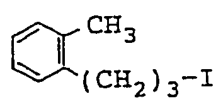
3-(4-Fluorophenyl)propyl iodide

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.79~2.35 (2H), 2.70 (2H, t, J=7Hz), 3.13 (2H, t, J=6Hz), 6.55~7.45 (4H).

Ref. Ex. 86



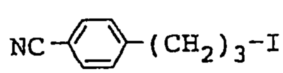
3-(2-Methylphenyl)propyl iodide

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.90~2.47 (2H), 2.32 (3H, s), 2.55~2.90 (2H), 3.22 (2H, t, J=6Hz), 7.11 (4H, s).

Ref. Ex. 87



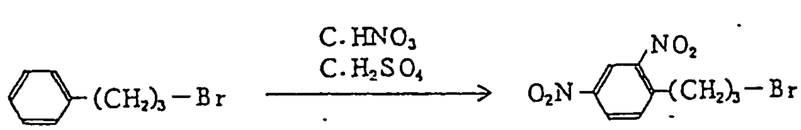
3-(4-Cyanophenyl)propyl iodide

Physicochemical Properties

MMR ($CDCl_3$)

δ: 1.86~2.42 (2H), 2.14~3.00 (2H), 3.16 (2H, t, J=6Hz), 7.13~7.71 (4H).

REFERENCE EXAMPLE 88



Phenylpropyl bromide (5.01 g) was added dropwise to a mixture of 10 ml of concentrated nitric acid (65%) and 10 ml of concentrated sulfuric acid with ice cooling over 5 minutes. The mixture was stirred at the same temperature for 1 hour and then allowed to stand at room temperature for 1 week. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. The residue was subjected to silica gel column chromatography (150 g). Elution with hexane-ethyl acetate (10:1) gave 5.50 g of 2,3-dinitrophenylpropyl bromide.

NMR ($CDCl_3$)

δ: 2.08~2.51 (2H) 3.20 (2H, dd, J=7Hz, J=9Hz) 3.50 (2H, t, J=6Hz) 7.68 (1H, d, J=9Hz) 8.42 (1H, dd, J=3Hz, J=9Hz) 8.79 (1H, d, J=3Hz)

REFERENCE EXAMPLE 89

A solution of 0.51 g of 3-(4-aminophenyl)propanol in 5 ml of 47% aqueous hydrobromic acid was refluxed for 6 hours. The solvent was then distilled off under reduced pressure. Methanol and toluene were added, and the solvents were distilled off under reduced pressure, and this procedure was repeated, whereupon 1.04 g of 3-(4-aminophenyl)propyl bromide hydrobromide was obtained.

NMR (DMSO-d_6+$CDCl_3$ (3:1))

δ: 1.91~2.47 (2H) 2.64~3.03 (2H) 3.43 (2H, t, J=6Hz) 4.85 (3H, br s) 7.40 (4H, s)

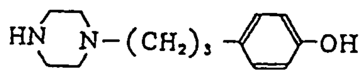
REFERENCE EXAMPLES 90 TO 100

The following compounds were obtained in the same manner as in Reference Example 33 (2) and (3).

Desired Product

Chemical Structure
and Chemical Name

Ref. Ex. 90



1-[3-(4-Hydroxyphenyl)-
propyl]piperazine

Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.92~1.84 (2H, m)

2.04~2.93 (12H, m)

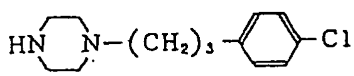
4.50~5.20 (2H, br)

6.65 (1H, d, J=9Hz)

6.96 (1H, d, J=9Hz)

2) MS: m/z 216 (M^+)

Ref. Ex. 91



1-[3-(4-Chlorophenyl)-
propyl]piperazine

Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.50~2.05 (2H, m)

1.64 (1H, s)

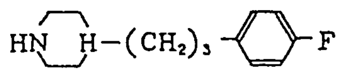
2.06~3.01 (8H, m)

2.90 (4H, t, J=5Hz)

6.80~7.51 (4H, m)

2) MS: m/z 238, 240 (M^+)

Ref. Ex. 92



1-[3-(4-Fluorophenyl)-propyl]piperazine

Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.56~2.04 (2H, m)

1.80 (1H, s)

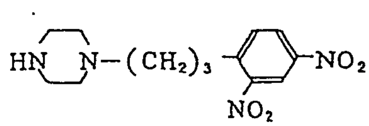
2.19~2.78 (8H, m)

2.95 (4H, t, J=5Hz)

6.80~7.36 (4H, m)

2) MS: m/z 223 (M^{+}+1)

Ref. Ex. 93



1-[3-(2,4-Dinitrophenyl)-propyl]piperazine

Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.64~2.13 (2H, m)

2.04 (1H, s)

2.22~2.53 (6H, m)

2.88 (4H, t, J=5Hz)

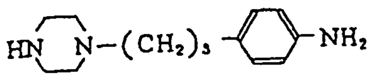
3.05 (2H, t, J=7Hz)

7.61 (1H, d, J=9Hz)

8.38 (1H, dd, J=3Hz, 9Hz)

8.64 (1H, dd, J=3Hz)

Ref. Ex. 94



1-[3-(4-Aminophenyl)-propyl]piperazine

Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.56~1.93 (2H, m)

2.18~2.64 (11H, m)

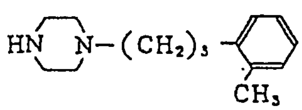
2.89 (4H, t, J=5Hz)

6.60 (2H, d, J=9Hz)

6.95 (2H, d, J=9Hz)

2) MS: m/z 219 (M^+)

Ref. Ex. 95



1-[3-(2-Methylphenyl)-propyl]piperazine

Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.53~1.92 (2H, m)

2.28 (3H, s)

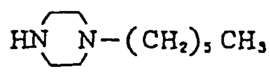
2.20~2.70 (8H, m)

2.88 (4H, t, J=5Hz)

7.09 (4H, s)

2) MS: m/z 218 (M^+)

Ref. Ex. 96



1-Hexylpiperazine

Physicochemical Properties

NHR ($CDCl_3$)

δ: 0.90 (3H, t)

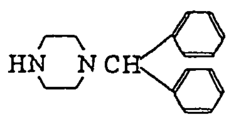
1.12~1.72 (8H, m)

2.20~2.52 (6H, m)

2.82~3.00 (4H, m)

MS: m/z 170 (M^+)

Ref. Ex. 97



1-Diphenylmethylpiperazine

Physicochemical Properties

NMR ($CDCl_3$)

δ: 2.20~2.48 (4H, m)

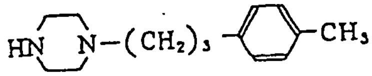
2.76~3.04 (4H, m)

4.23 (1H, s)

7.04~7.52 (10H, m)

MS: m/z 252 (M^+)

Ref. Ex. 98



1-[3-(4-Methylphenyl)-propyl]piperazine

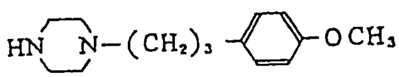
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.62~1.98 (2H, m),
1.76 (1H, s),
2.20~2.48 (6H, m),
2.35 (3H, s),
2.57 (2H, t, J=8Hz),
2.88 (4H, t, J=5Hz),
7.08 (4H, s).

MS: m/z 218 (M^+)

Ref. Ex. 99



1-[3-(4-Methylphenyl)-propyl]piperazine

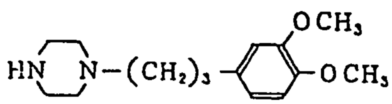
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.60~2.01 (2H, m),
1.92 (1H, s),
2.18~2.65 (8H, m),
2.87 (4H, t, J=5Hz),
3.77 (3H, s),
6.80 (1H, d, J=9Hz),
7.04 (1H, d, J=9Hz).

MS: m/z 234 (M^+)

Ref. Ex. 100



1-[3-(3,4-Dimethoxyphenyl)propyl]piperazine

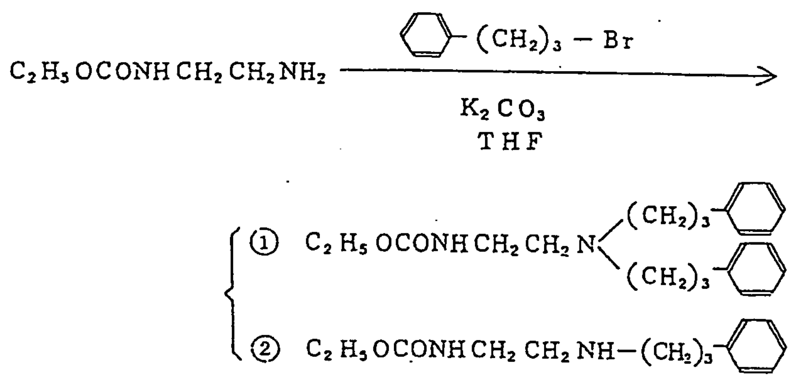
Physicochemical Properties

NMR ($CDCl_3$)

δ: 1.58~2.00 (2H, m),
1.86 (1H, s),
2.23~2.71 (8H, m),
2.91 (4H, t, J=5Hz),
3.84 (6H, s),
6.60~6.90 (3H, m).

MS: m/z 264 (M^+)

REFERENCE EXAMPLE 101

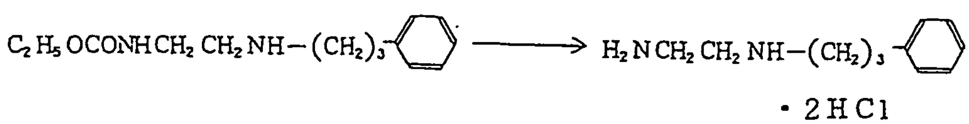


A solution of 0.88 g of carboethoxyethylenediamine, 1.33 g of 3-phenylpropyl bromide and 1.0 g of anhydrous potassium carbonate in 10 ml of tetrahydrofuran was heated overnight under reflux. The insoluble matter was filtered off, the filtrate was concentrated under reduced pressure, and the residue was subjected to alumina column chromatography (25 g). Elution with hexane-ethyl acetate (3:1 v/v) gave 0.54 g of N-carboethoxy-N',N'-bis(3-phenylpropyl)ethylenediamine (1) and 0.60 g of N-carboethoxy-N'-(3-phenylpropyl)ethylenediamine (2).

NMR ($CDCl_3$)
δ: 1.23 (3H, t, J=7Hz), 1.56~2.02 (4H, m), 2.20~2.87 (10H, m), 3.00~3.45 (2H, m), 4.12 (2H, t, J=7Hz), 5.13 (1H, br), 7.21 (10H, s)

NMR ($CDCl_3$)
δ: 1.21 (1H, s), 1.25 (3H, t, J=7Hz), 1.61~2.10 (2H, m), 2.45~2.93 (6H, m), 3.29 (2H, q, J=6Hz), 4.15 (2H, t, J=7Hz), 5.15 (1H, br), 7.21 (5H, s)

REFERENCE EXAMPLE 102



A solution of 580 mg of N-carboethoxy-N'-(3-phenylpropyl)ethylenediamine in 10 ml of concentrated hydrochloric acid was heated in a sealed tube at 120°C overnight. The mixture was concentrated under reduced pressure. Toluene was added and the mixture was again concentrated. Two repetitions of this procedure gave 630 mg of N-(3-phenylpropyl)ethylenediamine dihydrochloride. This product was submitted to the next step without purification.

NMR (DMSO-d_6)

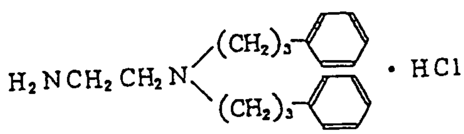
δ: 1.76~2.20 (2H,m), 2.48~3.10 (2H, m), 3.22 (4H, s), 7.28 (5H,2), 8.0~10.0 (5H,br).

MS: m/z 179 ($M^+ + 1$)

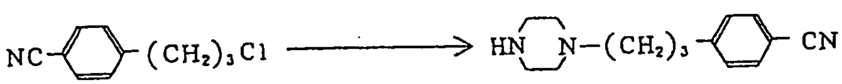
REFERENCE EXAMPLE 103

The following compound was obtained in the same manner as in Reference Examples 101 and 102.

Desired Product

Chemical Structure and Chemical Name	Physicochemical Properties
 N,N-Di(3-phenylpropyl)-ethylenediamine dihydrochloride	1) NMR (DMSO-d_6) δ: 1.76~2.24 (4H, m), 2.45~2.81 (4H, m), 2.92~3.60 (4H, m), 3.38 (4H, s), 7.26 (10H, s) 2) MS: m/z 297 (M^++1)

REFERENCE EXAMPLE 104



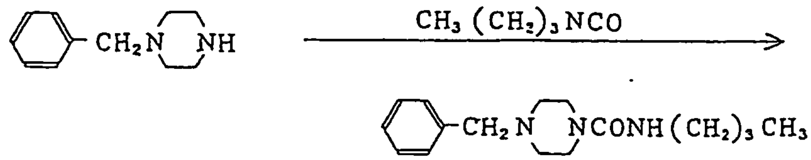
A solution of 250 mg of 3-(4-cyanophenyl)propyl iodide, 0.85 g of anhydrous piperazine and 0.5 g of potassium carbonate in 10 ml of tetrahydrofuran was refluxed for 2 hours. The reaction mixture was concen trated under reduced pressure and, after addition of saturated aqueous solution of sodium chloride, the residue was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 140 mg of 1-[3-(4-cyanophenyl)propyl]piperazine.

NMR ($CDCl_3$)

δ: 1.60~2.10 (2H, m), 2.04 (1H, s), 2.19~2.54 (6H, m), 2.69 (2H, t, J=8Hz), 2.89 (4H, t, J=5Hz), 7.27 (2H, d, J=9Hz), 7.56 (2H, d, J=9Hz)

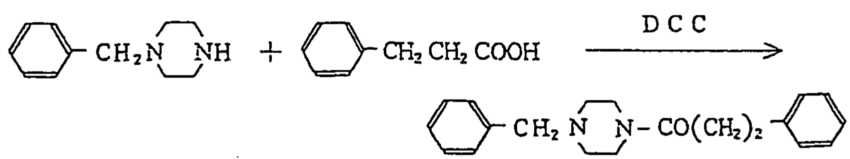
MS: m/z 229 (M^+)

REFERENCE EXAMPLE 105



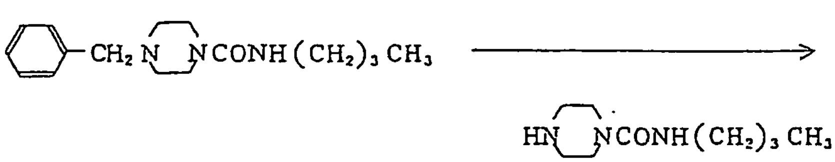
A solution of 1.0 g of n-butyl isocyanate in 5 ml of tetrahydrofuran was added to a solution of 1.76 g of 1-benzylpiperazine in 20 ml of tetrahydrofuran with ice cooling. The mixture was stirred at room temperature for 2 hours and, then, concentrated under reduced pressure to give 2.8 g of crude 1-benzyl-4-butylaminocarbonylpiperazine. The intermediate was submitted to the next step without purification.
NMR $CDCl_3$)
δ: 0.90 (3H, t), 1.1 ~ 1.7 (4H, m), 2.2 ~ 2.6 (4H, m), 3.0 ~ 3.6 (6H, m), 3.50 (2H, s), 4.5 (1H, br s), 7.0 ~ 7.5 (5H, m)

REFERENCE EXAMPLE 106



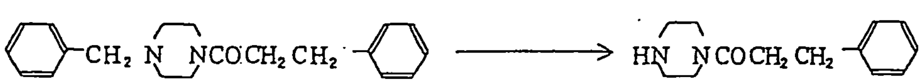
Dicyclohexylcarbodiimide (4.5 g) was added to a mixture of 3.52 g of 1-benzylpiperazine, 3.5 g of 3-phenylpropionic acid and 20 ml of tetrahydrofuran, and the mixture was stirred overnight at room temperature. The resultant dicyclohexylurea was filtered off, and the mother liquor was concentrated under reduced pressure. Ethyl acetate (100 ml) and 50 ml of water were added to the residue, and the mixture was made alkaline with potassium carbonate and then allowed to undergo phase separation. The ethyl acetate layer was washed in sequence with water and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 6 g of 1-benzyl-4-(3-phenylpropionyl)piperazine.
NMR ($CDCl_3$)
δ: 2.1 ~ 2.5 (4H, m), 2.4 ~ 3.2 (4H, m), 3.3 ~ 3.8 (4H, m), 3.45 (2H, s), 7.1 ~ 7.4 (10H, m)

REFERENCE EXAMPLE 107



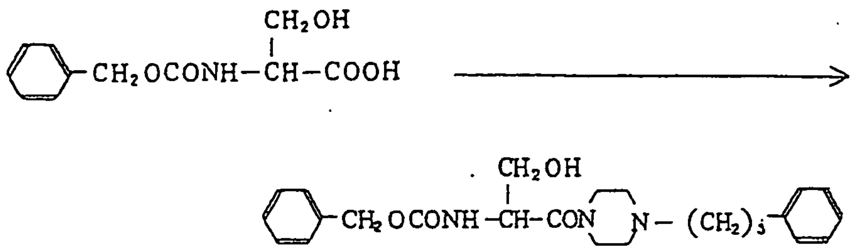
10% Palladium-on-carbon (250 mg) was added to a solution of 2.8 g of 1-benzyl-4-butylaminocarbonylpiperazine in 15 ml of ethanol, and catalytic reduction was carried out until cessation of hydrogen absorption. The catalyst was then filtered off, and the filtrate was concentrated under reduced pressure to give 2.2 g of 1-butylaminocarbonylpiperazine. This product was submitted to the next step without purification.
NMR ($CDCl_3$)
δ: 0.92 (3H, t), 1.1 ~ 1.7 (4H, m), 2.7 ~ 3.0 (4H, m), 3.0 ~ 3.5 (6H, m)

REFERENCE EXAMPLE 108



1-(3-Phenylpropionyl)piperazine was obtained in the same manner as in Reference Example 107 using 1-benzyl-4-(3-phenylpropionyl)piperazine as the starting material.
MS: m/z 218 (M^+)

REFERENCE EXAMPLE 109

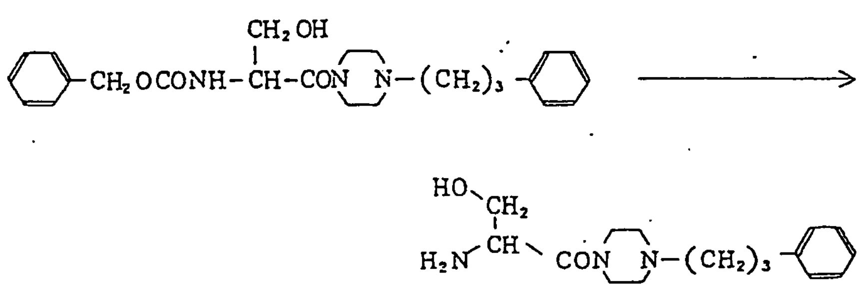


Dicyclohexylcarbodiimide (1.58 g) was added to an ice-cooled solution of 2.0 g of N-carbobenzyloxyserine, 1.57 g of 1-(3-phenylpropyl)piperazine and 1.04 g of 1-hydroxybenzotiazole in 30 ml of N,N-dimethylformamide. The mixture was stirred at room temperature for 24 hours, then diluted with ethyl acetate, washed in sequence with two portions of 4% aqueous sodium hydrogen carbonate, one portion of water and one portion of saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 2.39 g of 1-[2-(benzyloxycarbonylamino)-3-hydroxypropionyl]-4-(3-phenylpropyl)piperazine. Melting point 95-97°C

Elemental analysis (for $C_{24}H_{31}N_3O_4$):

	C (%)	H (%)	N (%)
Calculated:	67.74	7.34	9.87
Found:	67.74	7.26	9.88

REFERENCE EXAMPLE 110



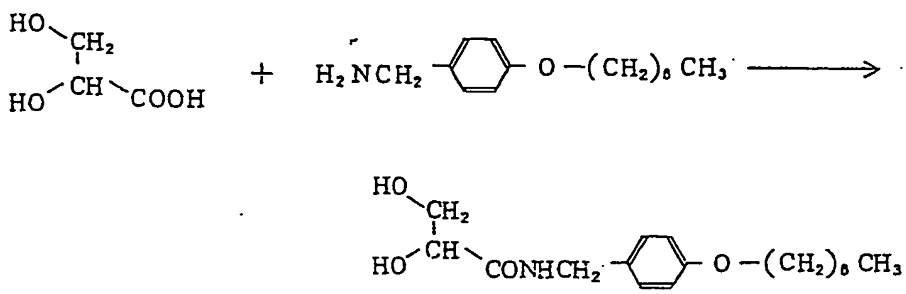
10% Palladium-on-carbon (100 mg) was added to a solution of 1.12 g of 1-[2-(benzyloxycarbonylamino)-3-hydroxypropionyl]-4-(3-phenylpropyl)piperazine in 30 ml of ethanol, and the mixture was stirred under a hydrogen gas stream until cessation of hydrogen absorption. The catalyst was then filtered off, and the filtrate was concentrated under reduced pressure to give 800 mg of 1-(2-amino-3-hydroxypropionyl)-4-(3-phenylpropyl)piperazine.

NMR ($CDCl_3$)

δ: 1.7~2.0 (2H), 1.8~2.6 (3H, exchange with D_2O), 2.3~2.8 (8H), 3.4~3.8 (7H), 7.1~7.3 (5H)

MS: m/z 291 (M^+)

REFERENCE EXAMPLE 111



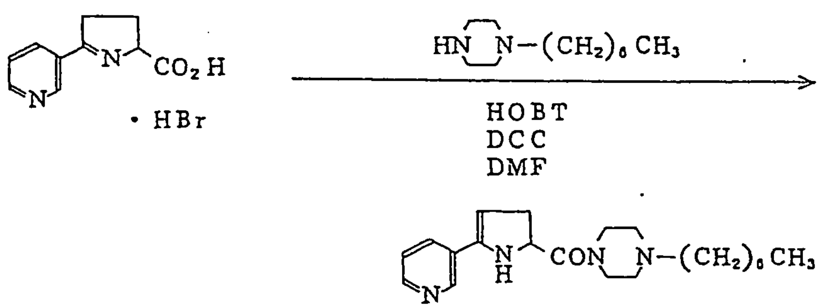
Dicyclohexylcarbodiimide (160 mg) was added to a solution of 200 mg of p-heptyloxybenzylamine, 150 mg of glyceric acid (65% aqueous solution) and 110 mg of 1-hydroxybenzotriazole in 2 ml of N,N-dimethylformamide. The reaction mixture was stirred at room temperature for 16 hours, then diluted with ethyl acetate, washed in sequence with saturated aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by preparative silica gel thin layer chromatography to give 80 mg of N-(p-heptyloxybenzyl)glyceramide.

NMR ($CDCl_3$)

δ: 0.90 (3H, br t), 1.2~1.5 (8H), 1.7~1.9 (2H), 3.0 (1H, exchange with D_2O), 3.8~4.0 (2H), 3.9 (1H, exchange with D_2O), 4.1~4.3 (1H), 4.38 (2H, d, J=6Hz), 6.88 (2H, d, J=8Hz), 7.18 (2H, d, J=8Hz), 7.0~7.3 (1H, exchange with D_2O)

MS: m/z 309 (M^+)

REFERENCE EXAMPLE 112



A mixture of 1.15 g of 2-(3-pyridyl)-1-pyrroline-4-carboxylic acid monohydrobromide, 770 mg of 1-heptylpiperazine, 860 mg of dicyclohexylcarbodiimide and 560 mg of 1-hydroxybenzotriazole in 15 ml of N,N-dimethylformamide was stirred at room temperature for 3 days. After dilution of the reaction mixture with ethyl acetate, the insoluble matter was filtered off, the filtrate was concentrated under reduced pressure and, after addition of 0.5 N aqueous sodium hydroxide, the residue was extracted with ethyl acetate. The organic layer was extracted with 1 N hydrochloric acid. The aqueous layer was adjusted to pH 10 by addition of potassium carbonate and extracted again with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (15 g). Elution with ethyl acetate gave 1.01 g of 1-heptyl-4-[2-(3-pyridyl)-2-pyrrolin-5-ylcarbonyl]piperazine.

NMR ($CDCl_3$)

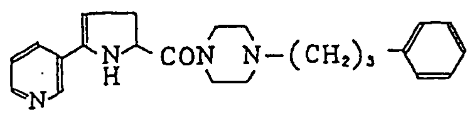
δ: 0.91 (3H, t, J=6Hz), 1.12~1.72 (10H, m), 1.92~2.93 (9H, m), 2.95~3.26 (2H, m), 3.37~4.30 (3H, m), 5.04.5.30 (1H, m), 7.26~7.46 (1H, ddd, J=1HZ, J=5HZ, J=8Hz), 8.18 (1H, dt, J=2HZ, J=8Hz), 8.68 (1H, dd, J=2HZ, J=5Hz), 9.05 (1H, dd, J=1HZ, J=2Hz)

MS: m/z 356 (M^+)

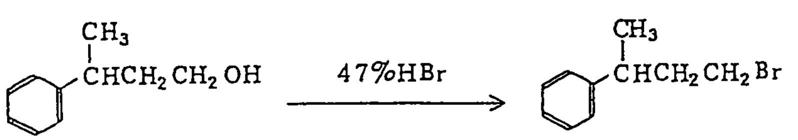
REFERENCE EXAMPLE 113

The following compounds was obtained in the same manner as in Reference Example 112.

Desired Product

Chemical Structure and Chemical Name	Physicochemical Properties
 1-(3-Phenylpropyl)-4-[2-(3-pyridyl)-2-pyrrolin-5-ylcarbonyl]piperazine	1) NMR ($CDCl_3$) δ: 1.67~2.08 (2H, m), 2.08~2.93 (9H, m), 2.93~3.28 (2H, m), 3.30~4.32 (3H, m), 5.00~5.33 (1H, m), 7.05~7.52 (6H, m), 8.19 (1H, dt, J=2Hz, J=8Hz), 8.69 (1H, dd, J=2Hz, J=5Hz), 9.05 (1H, dd, J=2Hz, J=2Hz) 2) MS: m/z 376 (M^+)

REFERENCE EXAMPLE 114



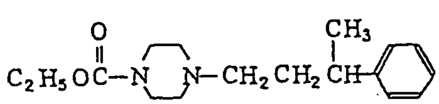
1-Bromo-3-phenylbutane was obtained in the same manner as in Reference Example 80.

NMR $CDCl_3$)

δ: 1.29 (3H, d, J=7Hz), 2.11 (2H, q, J=7Hz), 2.64~3.50 (3H, m), 7.24 (5H, s)

REFERENCE EXAMPLE 115

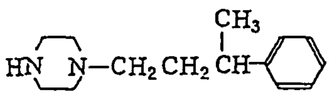
The following compound was obtained in the same manner as in Reference Example 101.



Ethyl 4-(3-phenylbutyl)-piperazine-1-carboxylate
NMR ($CDCl_3$)
δ: 1.11~1.50 (6H, m), 1.56~3.05 (7H, m), 3.50 (4H, t, J=6Hz), 4.19 (2H, q, J=7Hz), 7.24 (5H, s)

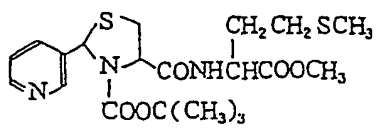
REFERENCE EXAMPLE 116

The following compound was obtained in the same manner as in Reference Example 102.



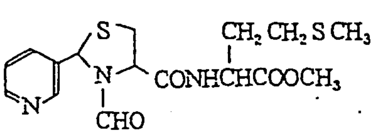
1-(3-Phenylbutyl)piperazine
NMR ($CDCl_3$)
δ: 1.24 (3H, d, J=7Hz), 1.76 (2H, q, J=7Hz), 1.93 (1H, s), 2.10~2.46 (6H, m), 2.51~2.97 (5H, m), 7.00~7.38 (5H, m)
MS (m/z): 218 (M^+)

EXAMPLE 1



To a solution of 600 mg of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid in 10 ml of tetrahydrofuran, there were added, at 4°C or below, 390 mg of L-methionine methyl ester hydrochloride, 390 mg of 1-hydroxybenzotriazole, 190 mg of N-methylmorpholine and 440 mg of dicyclohexylcarbodiimide, in that order. The mixture was stirred at 4°C or below for 1 hour and then at room temperature for 1 hour. The resultant precipitate was filtered off, the filtrate was concentrated under reduced pressure, 50 ml of ethyl acetate was added, the insoluble matter was filtered off, and the filtrate was washed in sequence with 0.5 M aqueous citric acid, water, 5% aqueous sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 440 mg of [N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carbonyl]-L-methionine methyl ester as an oil.
NMR ($CDCl_3$)
δ: 1.36 (9H, s), 1.8~2.2 (3H, m), 2.2~2.6 (2H, m), 3.26 (1H, dd), 3.6 (1H, dd), 3.78 (3H, s), 4.6~4.8 (1H, m), 4.86 (1H, dd), 6.02 (1H, s), 7.3 (1H, dd), 7.8~8.0 (1H, m), 8.52 (1H, dd), 8.65 (1H, dd)

EXAMPLE 2

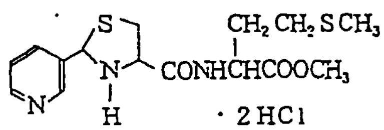


To a solution of 1.3 g of N-formyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid in 50 ml of tetrahydrofuran plus 10 ml of N,N-dimethylformamide, there were added, at 4°C or below, 1.16 g of L-methionine methyl ester hydrochloride, 1.17 g of 1-hydroxybenzotriazole, 560 mg of N-methylmorpholine and 1.32 g of dicyclohexylcarbodiimide, in that order. The mixture was stirred at 4°C or below for 1 hour and then at room temperature for 1 hour. The reaction mixture was then treated in the same manner as in Example 1. Purification by silica gel column chromatography [eluent: chloroform-methanol (9:1)] gave 820 g of [N-formyl-2-(3-pyridyl)thiazolidine-4-carbonyl]-L-methionine methyl ester as an oil.
Elemental analysis (for $C_{16}H_{21}N_3O_4S_2$)

	N (%)
Calculated:	10.96
Found:	10.62

NMR ($CDCl_3$)
δ: 2.08 (3H, s), 1.8~2.6 (4H, m), 3.2~3.5 (1H, m), 3.8 (3H, s), 3.5~3.8 (1H, m), 4.5~4.8 (1H, m), 4.8~5.1 (1H, m), 6.1 and 6.41 (s, respectively 1H), 7.2~7.5 (1H, m), 7.8~8.0 (1H, m), 8.34 (1H, s), 8.4~8.9 (2H, m)

EXAMPLE 3

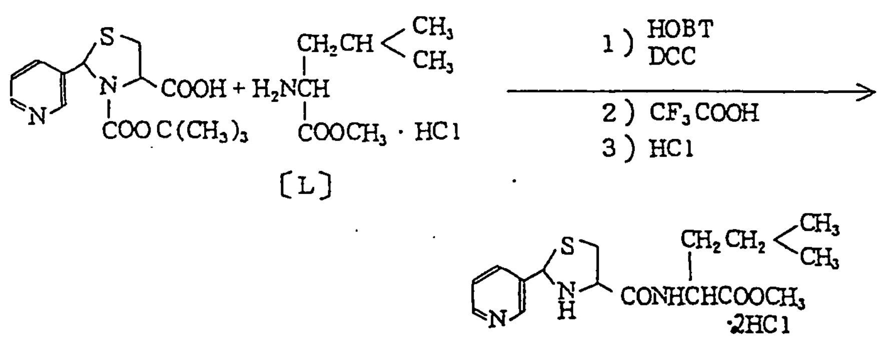


Trifluoroacetic acid (5 ml) was added to 430 mg of [N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carbonyl]-L-methionine methyl ester with ice cooling, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, and the mixture was again concentrated under reduced pressure. The residue was dissolved in 5 ml of ethyl acetate, and 1 ml or 4 N hydrochloric acid in dioxane was added with ice cooling. The resultant crystalline precipitate was collected by filtration, washed with ethyl acetate and dried to give 300 mg of [2-(3-pyridyl)thiazolidine-4-carbonyl] L-methionine methyl ester dihydrochloride. Melting point 110°C.

Elemental analysis (for $C_{15}H_{25}N_3O_4S_2Cl_2$):

	C (%)	H (%)	N (%)
Calculated:	40.36	5.64	9.41
Found:	40.00	5.35	9.24

EXAMPLE 4



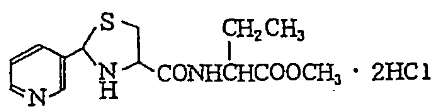
To a solution of 600 mg of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid in 5 ml of tetrahydrofuran, there were added, at 4° C or below, 350 mg of L-leucine methyl ester hydrochloride, 390 mg of 1-hydroxybenzotriazole, 190 mg of N-methylmorpholine and 440 mg of dicyclohexylcarbodiimide, in that order, and the mixture was stirred overnight in an icehouse. The resultant precipitate was filtered off, the filtrate was concentrated under reduced pressure, 50 ml of ethyl acetate was added, the insoluble matter was filtered off,

and the filtrate was washed in sequence with 0.5 M aqueous citric acid, water, saturated aqueous solution of sodium hydrogen carbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 830 mg of oily [N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carbonyl]-L-leucine methyl ester. Trifluoroacetic acid (3 ml) was added to 800 mg of the thus-obtained compound with ice cooling, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, 10 ml of ethyl acetate was added and the solution was again concentrated under reduced pressure. The residue was dissolved in 10 ml of ethyl acetate, 3 ml of 2.2 N hydrogen chloride solution in dioxane was added with ice colling, and the mixture was allowed to stand overnight in an icehouse. The resultant crystals were collected by filtration, washed with ethyl acetate and dried to give 510 mg of [2-(3-pyridyl)thiazolidine-4-carbonyl]-L-leucine methyl ester dihydrochloride. Melting point 97-100°C.

Elemental analysis (for $C_{16}H_{23}N_3O_3S \bullet 2HCl \bullet {}^4/_5H_2O$)

	C (%)	H (%)	N (%)	S (%)
Calculated:	45.24	6.31	9.89	7.55
Found:	45.21	5.98	9.85	7.55

EXAMPLE 5

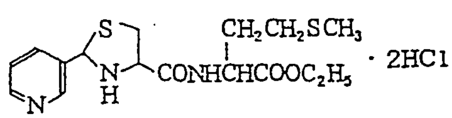


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and D,L-α-aminobutyric acid methyl ester hydrochloride were used as the starting materials and treated in the same manner as in Example 4 to give 2-[2-(3-pyridyl)thiazolidin-4-yl]carbonylaminobutyric acid methyl ester dihydrochloride. Melting point 98-100°C.

Elemental analysis (for $C_{14}H_{19}N_3O_3S \bullet 2HCl \bullet H_2O$)

	C (%)
Calculated:	42.00
Found:	42.08

EXAMPLE 6

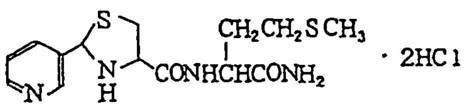


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and D-methionine ethyl ester hydrochloride were used as the starting materials and treated in the same manner as in Example 4 to give [2-(3-pyridyl)thiazolidine-4-carbonyl]-D-methionine ethyl ester dihydrochloride. Melting point 94-96°C.

Elemental analysis (for $C_{16}H_{23}N_3O_3S_2 \bullet 2HCl \bullet 4/5H_2O$)

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	42.07	5.87	9.20	14.04	15.52
Found:	42.17	5.89	8.89	13.77	15.68

EXAMPLE 7



N-tert-Butoxycarbonyl-2-(3 pyridyl)thiazolidine-4-carboxylic acid and L-methioninamide hydrochloride were used as the starting materials and treated in the same manner as in Example 4 to give [2-(3-pyridyl)thiazolidine-4-carbonyl]-L-methioninamide dihydrochloride. Melting point 131°C.

MS: m/z 340 (M^+-2HCl)

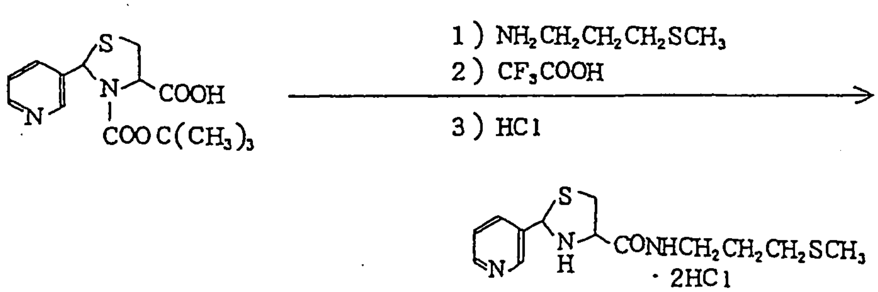
EXAMPLE 8

N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and glycine methyl ester hydrochloride were used as the starting materials and treated in the same manner as in Example 4 to give [2-(3-pyridyl)thiazolidine-4-carbonyl]glycine methyl ester dihydrochloride. Melting point 116-118°C.

Elemental analysis (for $C_{12}H_{15}N_3O_3S{\bullet}2HCl{\bullet}H_2O$)

	C (%)	H (%)	N (%)
Calculated:	38.72	5.14	11.29
Found:	38.99	4.62	10.99

EXAMPLE 9



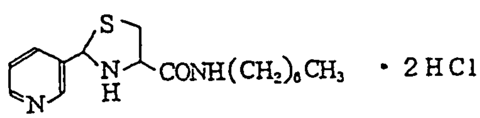
To a solution of 600 mg of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid in 10 ml of tetrahydrofuran, there were added, at 4°C or below, 200 mg of 3-methylthiopropylamine, 390 mg of

1-hydroxybenzotriazole and 440 mg of dicyclohexylcarbodiimide, in that order, and the mixture was stirred at room temperature for 3 hours. The resultant precipitate was filtered off, the filtrate was concentrated under reduced pressure, and the residue was dissolved in 50 ml or ethyl acetate. The ethyl acetate solution was washed in sequence with 0.5 M aqueous citric acid, water, saturated aqueous solution of sodium carbonate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 250 mg of N-(3-methylthiopropyl)-3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxamide. Trifluoroacetic acid (2 ml) was added to 250 mg of the thus-obtained compound with ice cooling, and the mixture was treated in the same manner as in Example 4 to give 130 mg of N-(3-methylthiopropyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride as an oil.

NMR (DMSO-d_6)

δ: 1.6~1.9 (2H), 2.08 (3H), 2.4~2.6 (2H), 3.0~3.7 (4H), 4,05~4.50 (1H), 5.9~6.1 (1H), 7.4~9.2 (4H)

EXAMPLE 10

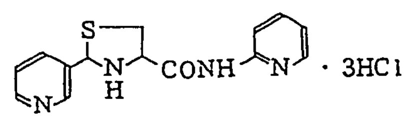


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and n-heptylamine were used as the starting materials and treated in the same manner as in Example 9 to give N-n-heptyl-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride.

NMR (DMSO-d_6)

δ: 0.6~1.1 (3H), 1.1~1.8 (10H), 2.9~3.9 (4H), 4.4~4.7 (1H), 6.20(1H), 8.0~8.3 (1H), 8.6~9.3 (3H)

EXAMPLE 11

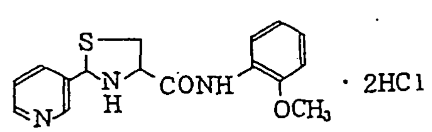


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and 2-aminopyridine were used and treated in the same manner as in Example 9 to give N-(2-pyridyl)-2-(3-pyridyl)thiazolidine-4-carboxamide trihydrochloride. Melting point 145°C.

Elemental analysis (for $C_{14}H_{17}N_4OSCl_3$)

	C (%)	H (%)	S (%)
Calculated:	42.49	4.33	8.10
Found:	42.83	4.58	8.03

EXAMPLE 12

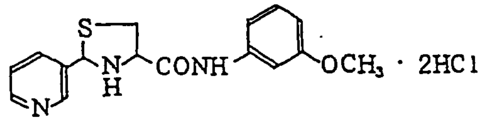


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and o-anisidine were used and treated in the same manner as in Example 9 to give N-(2-methoxyphenyl)-2-(3-pyridine)thiazolidine-4-carboxamide dihydrochloride. Yield, 68%. Melting point 129°C.

Elemental analysis (for $C_{16}H_{19}N_3O_2SCl_2$)

	C (%)	H (%)	N (%)
Calculated:	49.49	4.93	10.82
Found:	49.29	5.18	10.38

EXAMPLE 13

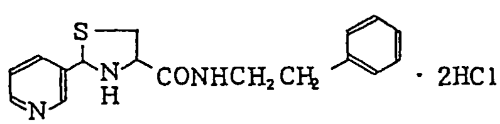


A mixture of 630 mg of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 350 mg of m-anisidine, 650 mg of dicyclohexylcarbodiimide and 430 mg of 1-hydroxybenzotriazole in 8 ml of dimethylformamide was stirred overnight at room temperature. The reaction mixture was diluted with 50 ml of ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed with two portions of water, and then with aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride in that order, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by preparative thin layer chromatography to give 230 mg of N-(3-methoxyphenyl)-2-(3-pyridyl)thiazolidine-4-carboxamide. This compound was dissolved in ethyl acetate, and 1 ml of 2 N hydrogen chloride solution in dioxâne was added. The resultant solid was collected by filtration, washed with ethyl acetate and dried to give 250 mg of N-(3-methoxyphenyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Melting point 129°C.

Elemental analysis (for $C_{16}H_{19}N_3O_2SCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	49.49	4.93	10.82	8.26
Found:	49.49	5.08	10.56	8.24

EXAMPLE 14

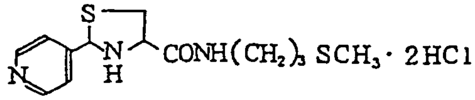


The procedure of Example 13 was followed using 2-(3-pyridyl)thiazolidine-4-carboxylic acid and 2-phenyl ethylamine to give N-(2-phenylethyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Yield, 81%. Melting point 115°C.

Elemental analysis (for $C_{17}H_{21}N_3OSCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	52.85	5.48	10.88	8.30
Found:	52.25	5.74	10.77	8.16

EXAMPLE 15



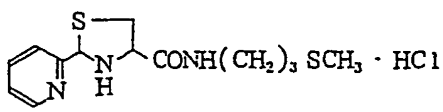
N-(3-Methylthiopropyl)-2-(4-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from the

compound obtained in Reference Example 2 and 3-methylthiopropylamine by following the procedure of Example 13. Melting point 70°C.

Elemental analysis (for $C_{13}H_{21}N_3OS_2Cl_2$):

	C (%)	H (%)	N (%)
Calculated:	42.16	5.72	11.35
Found:	41.65	5.83	10.87

Example 16

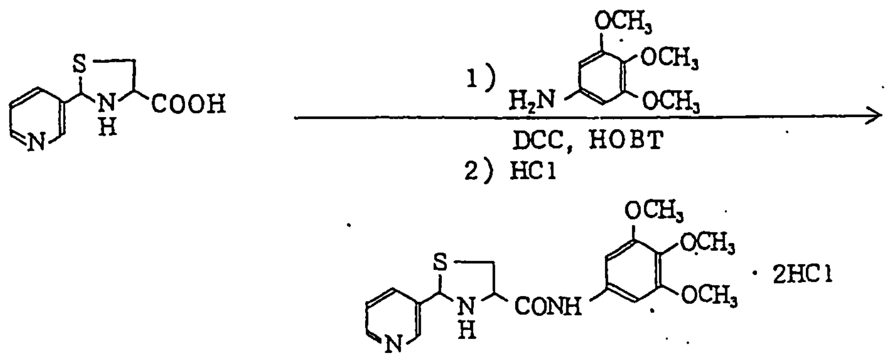


A solution of 1.50 g of pyridine-2-carboxaldehyde and 1.70 g of L-cysteine in 50% ethanol was stirred at room temperature for 4 hours. The insoluble matter was filtered off, and the filtrate reaction mixture was concentrated under reduced pressure. The thus-obtained syrupy substance was dissolved in 35 ml of tetrahydrofuran. To the solution were added 2.89 g of dicyclohexylcarbodiimide, 1.89 g of 1-hydroxybenzotriazole and 1.62 g of 3-methylthiopropylamine, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed with water (twice), aqueous sodium hydrogen carbonate, water (twice) and saturated aqueous solution of sodium chloride in that order, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by column chromatography (eluent: tolueneethyl acetate=1:1) to give 1.50 g of N-(3-methylthiopropyl)-2-(2-pyridyl)thiazolidine-4-carboxamide. A 800-mg portion of this compound was dissolved in ethyl acetate, and 2 N hydrogen chloride solution in dioxane was added. The solvent was distilled off, and the residue was dried to give 830 mg of N-(3-methylthiopropyl)-2-(2-pyridyl)thiazolidine-4-carboxamide hydrochloride. Melting point 65°C.

Elemental analysis (for $C_{13}H_{22}N_3O_2S_2Cl$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	44.37	6.30	11.94	18.22
Found:	44.59	6.09	11.79	18.38

EXAMPLE 17

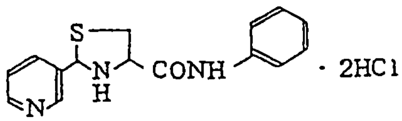


A mixture of 630 mg of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 520 mg of 3,4,5-trimethoxyaniline, 650 mg of dicyclohexylcarbodiimide and 430 mg of 1-hydroxybenzotriazole in 8 ml of N,N-dimethylformamide was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with aqueous sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (eluent: ethyl acetate) gave 370 mg of N-(3,4,5-trimethoxyphenyl)-2-(3-pyridyl)thiazolidine-4-carboxamide. This compound was dissolved in 10 ml of ethyl acetate, and 2 ml of 2 N hydrogen chloride solution in dioxane was added. The resultant solid was collected by filtration, washed with ethyl acetate and dried to give 200 mg of N-(3,4,5 trimethoxyphenyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Melting point 130-132°C.

Elemental analysis (for $C_{18}H_{23}N_3O_4SCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	48.22	5.17	9.37	7.15
Found:	48.23	5.35	9.02	7.12

EXAMPLE 18

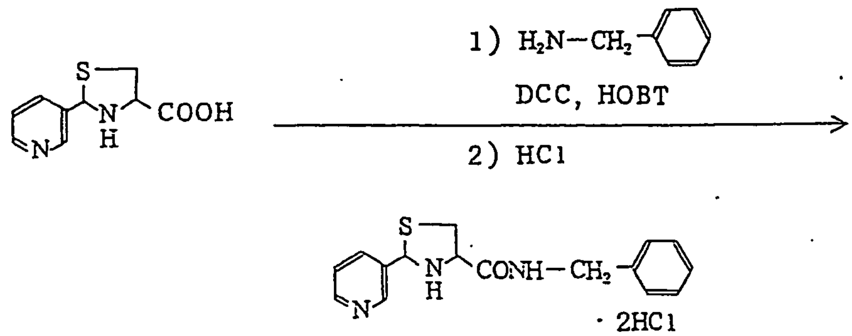


N-Phenyl-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and aniline by following the procedure of Example 17. Melting point 145-148°C.

NMR (DMSO-d_6)

δ: 3.4~4.2 (2H, 4.96 (1H, t), 6.31 and 6.35 (respectively 1H), 7.0~7.4 (3H), 7.6~7.8 (2H), 8.10 (1H, dd), 8.9~9.0 (2H), 9.3 (1H)

EXAMPLE 19

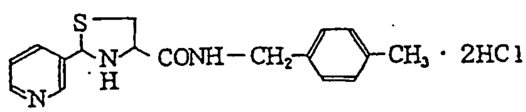


N-Benzyl-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and benzylamine by following the procedure of Example 17. Melting point 126-130°C.

NMR (DMSO-d_6)

δ: 3.2～3.7 (2H), 4.3～4.6 (3H), 6.08 and 6.14 (respectively 1H), 7.3 (5H), 8.06 (1H, dd), 8.7～9.0 (2H), 9.1～9.2 (1H)

EXAMPLE 20

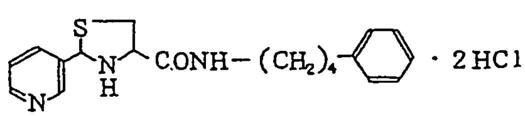


N-(p-Methylbenzyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and p-methylbenzyl amine by following the procedure of Example 17. Yield, 58%. Melting point 130-136°C.

Elemental analysis (for $C_{17}H_{21}N_3OSCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	52.85	5.48	10.88	8.30
Found:	52.64	5.56	10.81	8.38

EXAMPLE 21

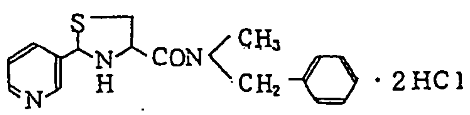


N-(4-Phenylbutyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and 4-phenylbutylamine by following the procedure of Example 17. Yield, 63%. Melting point 100-104°C.

Elemental analysis (for $C_{19}H_{25}N_3OSCl_2 \cdot 0.2H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	54.36	6.15	10.01	7.64	16.84
Found:	54.44	6.16	10.08	7.68	16.59

EXAMPLE 22

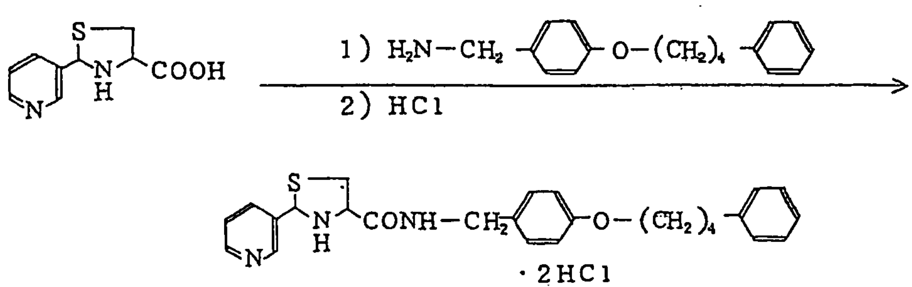


N-Benzyl-N-methyl-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and N-methylbenzylamine by following the procedure of Example 17. Melting point 105-110°C.

Elemental analysis (for $C_{17}H_{21}N_3OSCl_2 \bullet H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	50.50	5.73	10.39	7.93	17.54
Found:	50.63	5.60	10.43	7.98	17.26

EXAMPLE 23

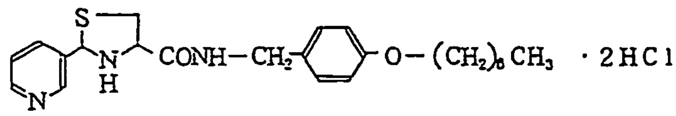


N-[p-(4-Phenylbutoxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and p-(4-phenylbutoxy)benzylamine by following the procedure of Example 17. Yield, 72%. Melting point 133-135°C.

Elemental analysis (for $C_{26}H_{31}N_3O_2SCl_2 \bullet 0.2H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	59.58	6.04	8.02	6.12	13.53
Found:	59.58	6.02	7.96	6.23	13.58

EXAMPLE 24

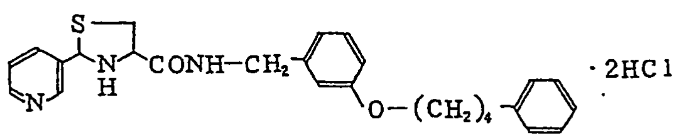


N-(p-Heptyloxybenzyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and p-heptyloxybenzylamine by following the procedure of Example 17. Melting point 155-160°C.

Elemental analysis (for $C_{23}H_{33}N_3O_2Cl_2 \cdot 0.3H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	56.16	6.88	8.54	6.52	14.41
Found:	56.11	6.84	8.47	6.53	14.50

EXAMPLE 25

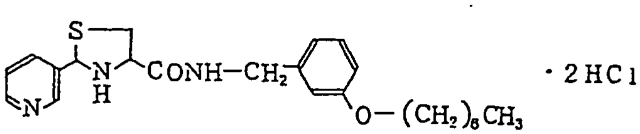


N-[m-(4-phenylbutoxy)benzyl]-2-(3-pyridyl)thiazolidine-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and m-(4-phenylbutoxy)benzylamine by following the procedure of Example 17. Yield, 41%. Melting point 88-93°C.

Elemental analysis (for $C_{26}H_{31}N_3O_2SCl_2 \cdot 0.5H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	58.97	6.09	7.94	6.06	13.39
Found:	58.96	6.07	7.96	6.11	13.36

EXAMPLE 26

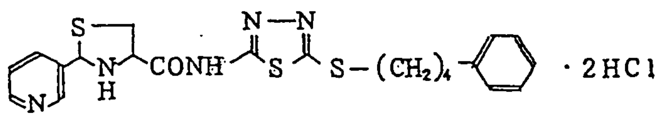


N-(m-Heptyloxybenzyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and m-heptyloxybenzylamine by following the procedure of Example 17. Melting point 135-140°C.

Elemental analysis (for $C_{23}H_{33}N_3O_2SCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	56.76	6.84	8,64	6.59
Found:	56.68	6.85	8.69	6.62

EXAMPLE 27

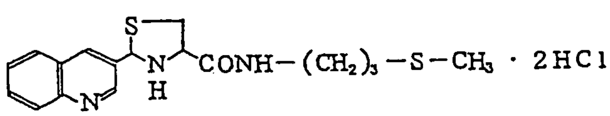


N-[5-[(4-phenylbutyl)thio]-1,3,4-thiadiazol-2-yl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-pyridyl)thiazolidine-4-carboxylic acid and 2-amino-5-[(4-phenylbutyl)thio]-1,3,4-thiadiazole by following the procedure of Example 17. Melting point 99-105°C.

Elemental analysis (for $C_{21}H_{26}OS_3Cl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	47.54	4.75	13.20	18.13
Found:	47.58	4.84	13.09	18.28

EXAMPLE 28

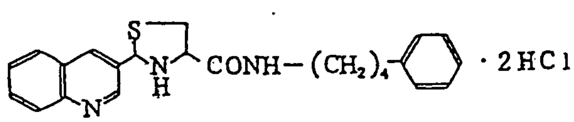


N-(3-Methylthiopropyl)-2-(3-quinolyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-quinolyl)thiazolidine-4-carboxalic acid and 3-methylthiopropylamine. Melting point 122-126°C.

Elemental analysis (for $C_{17}H_{23}N_3OS_2Cl_2 \cdot 0.5H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	47.55	5.63	9.78	14.93	16.51
Found:	47.57	5.72	9.75	15.02	16.47

EXAMPLE 29

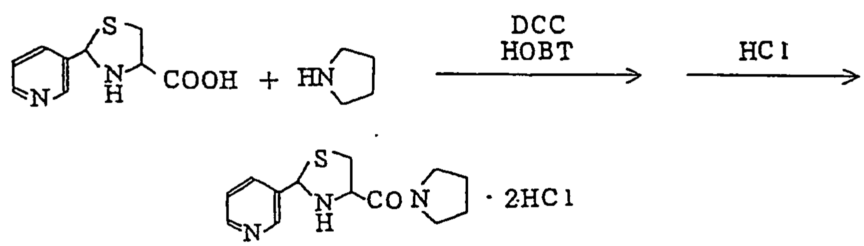


N-(4-Phenylbutyl)-2-(3-quinolyl)thiazolidine-4-carboxamide dihydrochloride was obtained from 2-(3-quinolyl)thiazolidine-4-carboxylic acid and 4-phenylbutylamine by following the procedure of Example 17. Yield, 53%. Melting point 116-122°C.

Elemental analysis (for $C_{23}H_{27}N_3OSCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	59.48	5.86	9.05	6.90
Found:	59.13	5.84	8.99	7.14

EXAMPLE 30

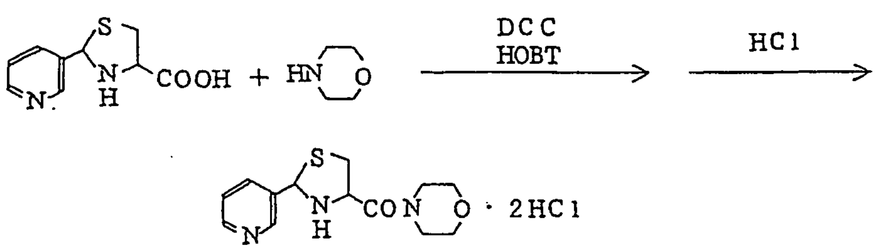


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and pyrrolidine were used as the starting materials and treated in the same manner as in Example 17 to give 1-[2- (3-pyridyl)thiazolidin-4-ylcarbonyl]pyrrolidine dihydrochloride. Melting point 136°C.

NMR (DMSO-d_6)

δ: 1.60 ~ 2.13 (4H, m), 3.0 ~ 3.90 (6H, m), 4.55 ~ 4.71 (1H, m), 6.09 and 6.26 (s, respectively 1H), 8.08 (1H, dd), 8.72 ~ 9.20 (3H, m)

EXAMPLE 31

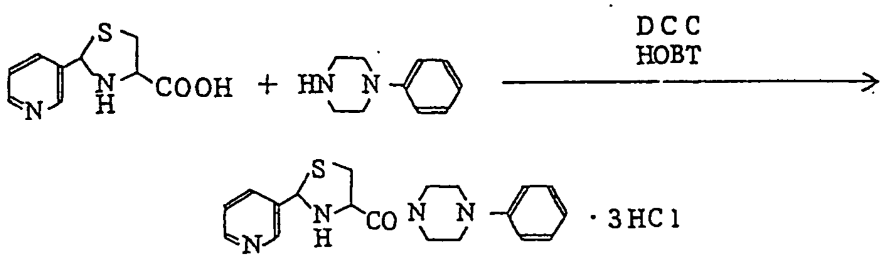


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and morpholine were used as the starting materials and treated in the same manner as in Example 17 to give 4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]morpholine dihydrochloride. Melting point 143°C.

NMR (DMSO-d_6)

δ: 2.97 ~ 3.78 (10H, m), 4.62 ~ 4.78 (1H, m), 6.00 and 6.23 (s, resepectively 1H), 8.05 (1H, dd), 8.71 ~ 9.10 (3H, m)

EXAMPLE 32

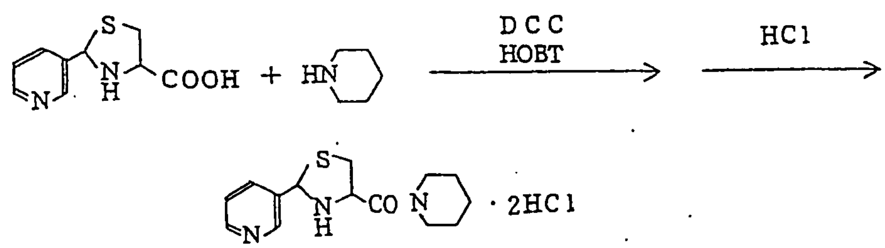


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and 1-phenylpiperazine were used as the starting materials and treated in the same manner as in Example 17 to give 1-phenyl-4-[2-(3-pyridyl)thiazolin-4-ylcarbonyl]piperazine trihydrochloride. Yield, 79%. Melting point 169°C.

NMR (DMSO-d_6)

δ: 3.04~4.20 (10H, m), 4.64~4.84 (1H, m), 6.00 and 6.23 (2, respectively 1H), 7.04~7.64 5H, m), 7.99~8.14 (1H, m), 8.70~9.16 (3H, m)

EXAMPLE 33

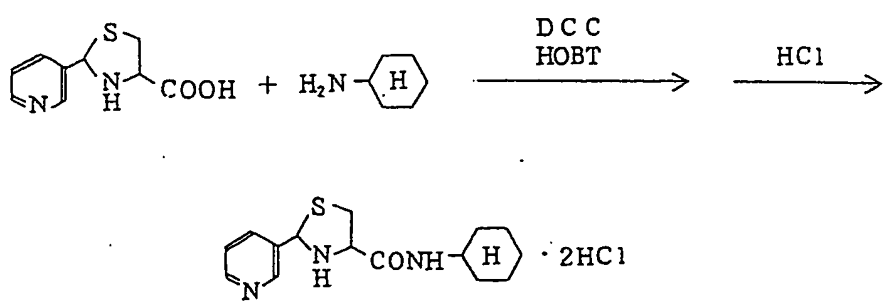


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and piperidine were used as the starting materials and treated in the same manner as in Example 17 to give 1-[2-(3-pyridyl)thiazolin-4-ylcarbonyl]piperidine dihydrochloride. Yield, 48%. Melting point 172°C.

Elemental analysis (for $C_{14}H_{21}N_3OSCl_2 \cdot 0.3H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	47.27	6.12	11.81	9.01	19.93
Found:	47.36	6.03	11.75	9.01	19.71

EXAMPLE 34



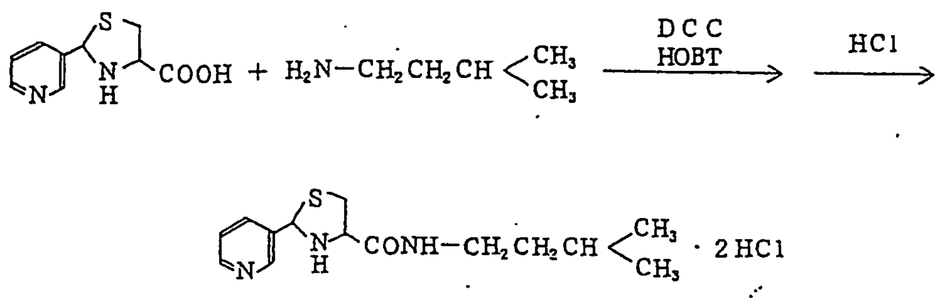
2-(3-Pyridyl)thiazolidine-4-carboxylic acid and cyclohexylamine were used as the starting materials and

treated in the same manner as in Example 17 to give N-cyclohexyl-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Melting point 139°C.

NMR (DMSO-d_6)

δ: 0.90~1.95 (11H, m), 3.06~3.69 (3H, m), 4.39 (1H, dd), 6.07 and 6.14 (s, respectively 1H), 8.03 (1H, dd), 8.46~9.13 (3H, m)

EXAMPLE 35

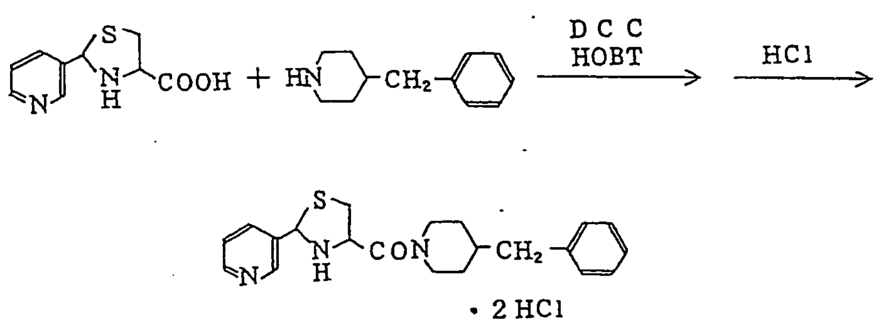


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and isoamylamine were used as the starting materials and treated in the same manner as in Example 17 to give N-(3-methylbutyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Yield, 47%. Melting point 115°C.

Elemental analysis (for $C_{14}H_{22}N_3OSCl_2 \cdot 0.3H_2O$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	47.14	6.39	11.78	8.99
Found:	47.24	6.59	11.56	9.10

EXAMPLE 36

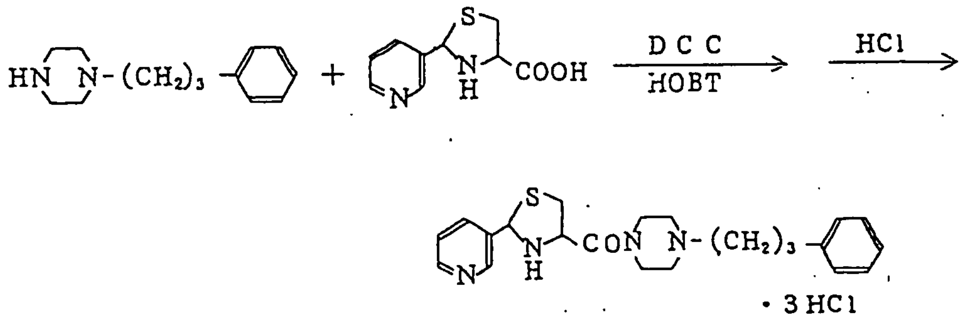


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and 4-benzylpiperidine were used as the starting materials and treated in the same manner as in Example 17 to give 4-benzyl-1-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperidine dihydrochloride. Yield, 60%. Melting point 135°C.

NMR (DMSO-d_6)

δ: 0.76~2.06 (5H, m), 2.35~4.54 (8H, m), 4.68~5.08 (1H, m), 6.08 and 6.28 (s, respectively 1H), 7.06~7.28 (5H, m), 8.07 (1H, dd), 8.71~9.30 (3H, m)

EXAMPLE 37

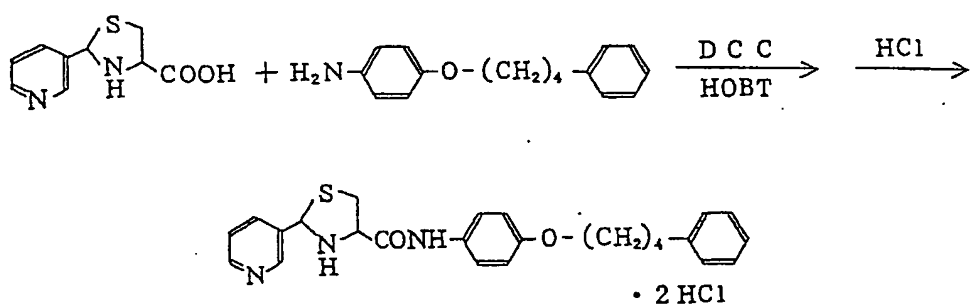


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and 1-(3 phenylpropyl)piperazine were used as the starting materials and treated in the same manner as in Example 17 to give 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride. Yield, 60%. Melting point 144°C.

NMR (DMSO-d_6)

δ: 1.85~4.86 (17H, m), 5.97 and 6.18 (s, respectively 1H), 7.10~7.48 (5H, m), 8.06 (1H, dd), 8.65~9.12 (3H, M)

EXAMPLE 38

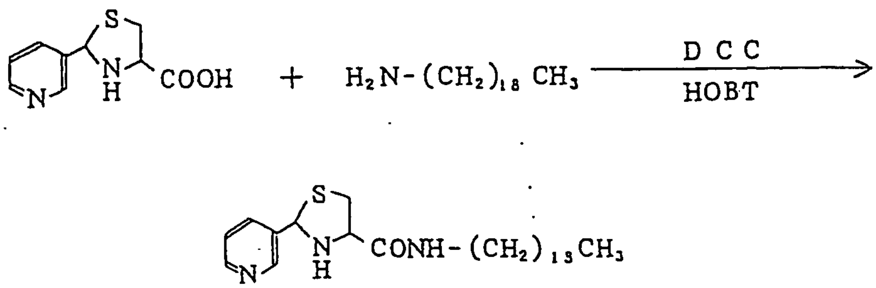


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and p-(4-phenylbutoxy)aniline were used as the starting materials and treated in the same manner as in Example 17 to give N-[p-(4-phenylbutoxy)phenyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Yield, 48%. melting point 117°C.

Elemental analysis (for $C_{25}H_{29}N_3O_2SCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	59.28	5.77	8.30	6.33
Found:	59.65	5.76	8.40	6.39

EXAMPLE 39

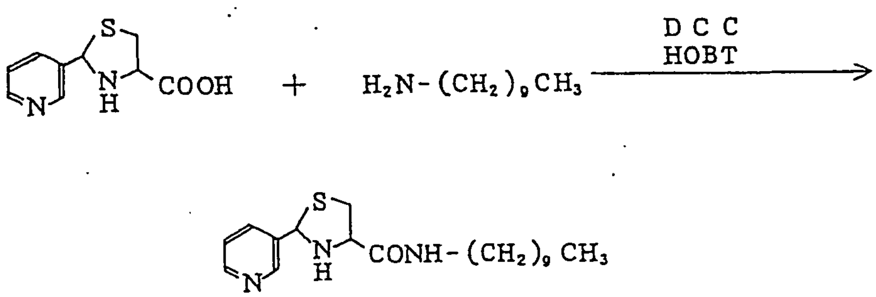


A solution of 500 mg of dicyclohexylcarbodiimide in 3 ml of tetrahydrofuran was added dropwise to a mixture of 510 mg of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 490 mg of 1-hydroxybenzotriazole, 680 mg of nonadecylamine and 12 ml of tetrahydrofuran with ice cooling, and the resulting mixture was stirred with ice cooling for 1 hour and then at room temperature for 12 hours. The reaction mixture was diluted with 30 ml of ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) and recrystallized from ethyl acetate to give 250 mg of N-nonadecyl-2-(3-pyridyl)thiazolidine-4-carboxamide. Melting point 108-110°C.

Elemental analysis (for $C_{28}H_{48}N_3OS \bullet 1/5H_2O$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	70.30	10.20	8.78	6.70
Found:	70.37	10.34	8.83	6.80

EXAMPLE 40

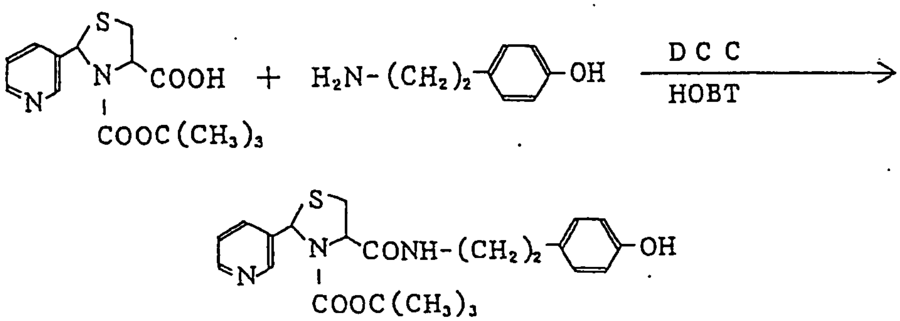


2-(3-Pyridyl)thiazolidine-4-carboxylic acid and decylamine were used as the starting materials and treated in the same manner as in Example 39 to give N-decyl-2-(3-pyridyl)thiazolidine-4-carboxamide. Yield, 80%. Melting point 88°C.

Elemental analysis (for $C_{19}H_{30}N_3OS$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	65.48	8.68	12.06	9.20
Found:	65.16	8.80	11.91	9.04

EXAMPLE 41

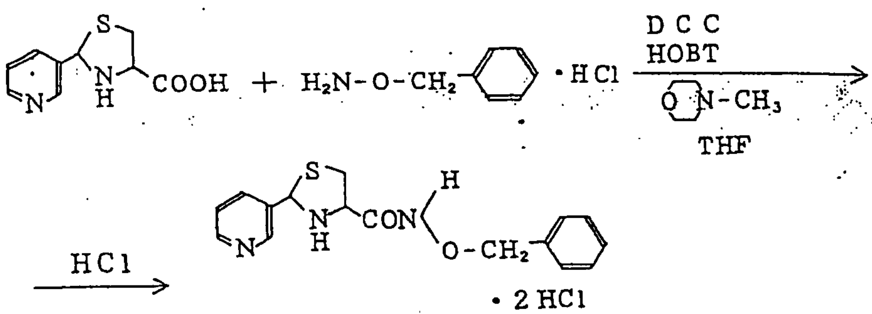


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and tyramine were used as the starting materials and treated in the same manner as in Example 39 to give N-[2-(p-hydroxyphenyl)ethyl]-3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxamide. Yield, 100%. Melting point 76°C.

NMR ($CDCl_3$)

δ: 1.34 (9H, s), 2.72 (2H, t), 3.22 (1H, dd), 3.43 ~ 3.70 (3H, m), 4.80 (1H, dd), 5.99 (1H, s), 6.70 ~ 7.03 (4H, m), 7.19 ~ 7.32 (1H, m), 7.75 ~ 7.84 (1H, m), 8.51 (1H, dd), 8.63 (1H, d)

EXAMPLE 42

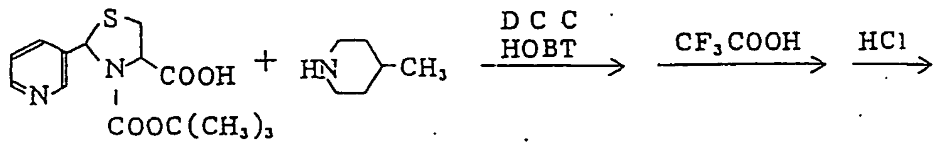


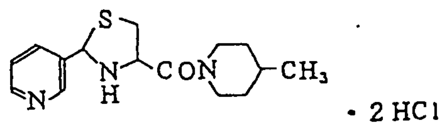
A solution of 490 mg of dicyclohexylcarbodiimide in 5 ml of tetrahydrofuran was added dropwise to a mixture of 500 mg of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 380 mg of O-benzylhydroxylamine, 480 mg of 1-hydroxybenzotriazole, 240 mg of N-methylmorpholine and 15 ml of tetrahydrofuran with ice cooling, and the resultant mixture was stirred with ice cooling for 1 hour and then at room temperature for 12 hours. The reaction mixture was diluted with 30 ml of ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (eluent: ethyl acetate) gave 260 mg of N-benzyloxy-2-(3-pyridyl)thiazolidine-4-carboxamide. This compound was dissolved in ethyl acetate, and 1.5 ml of 2 N hydrogen chloride solution in dioxane was added. The resultant solid was collected by filtration, washed with ethyl acetate and dried to give 240 mg of N-benzyloxy-2-(pyridin-3-yl)thiazolidine-4-carboxamide dihydrochloride. Melting point 115°C.

NMR (DMSO-d_6)

δ: 3.02 ~ 3.52 (2H, m), 4.07 ~ 4.20 (1H, m), 4.90 (2H, s), 6.00 and 6.08 (s, respectively 1H), 7.28 ~ 7.53 (5H, m), 8.07 (1H, dd), 8.64 ~ 9.26 (3H, m)

EXAMPLE 43



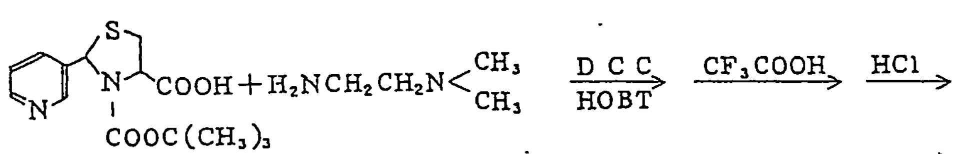


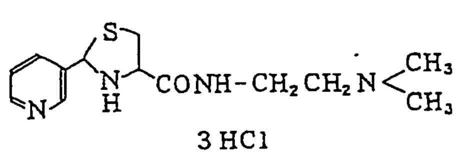
A solution of 540 mg of dicyclohexylcarbodiimide in 5 ml of tetrahydrofuran was added dropwise to a mixture of 810 mg of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid, 260 mg of 4-methylpiperidine, 530 mg of 1-hydroxybenzotriazole and 10 ml of tetrahydrofuran with ice cooling, and the mixture was stirred with ice cooling for 1 hour and then at room temperature for 12 hours. The reaction mixture was diluted with 30 ml of ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 4-methyl-1-[3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperidine. Trifluoroacetic acid (5 ml) was added to the thus-obtained compound, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (eluent: ethyl acetate) to give 4-methyl-1-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperid ine. This compound was dissolved in ethyl acetate, and 3 ml of 2 N hydrogen chloride solution in dioxane was added. The resultant solid was collected by filtration, washed with ethyl acetate and dried to give 530 mg of 4-methyl-1-[2-(3-pyridyl)thiazolidin-3-ylcarbonyl]piperidine dihydrochloride. Melting point 130°C.

Elemental analysis (for $C_{15}H_{23}N_3OSCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	49.45	6.39	11.53	8.80
Found:	49.59	6.60	11.47	8.63

EXAMPLE 44



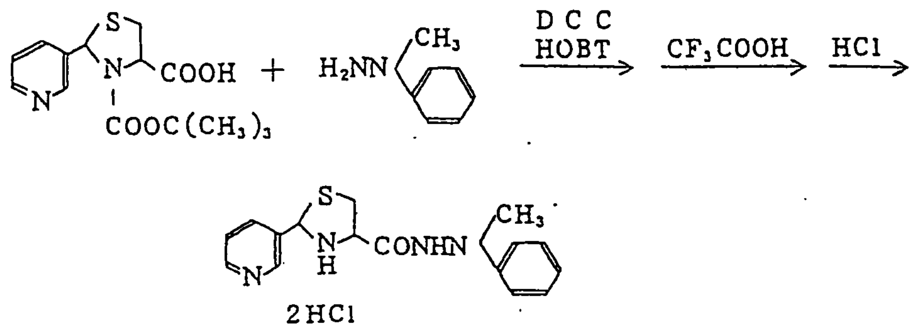


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and N,N-dimethylethylenediamine were used as the starting materials and treated in the same manner as in Example 43 to give N-[2-(N',N'-dimethylamino)ethyl]-2-(3-pyridyl)thiazolidine-4-carboxamide trihydrochloride. Melting point 150°C.

NMR (DMSO-d_6)

δ: 2.63 ~ 3.80 (12H, m). 4.26 ~ 4.50 (1H, m), 6.01 and 6.08 (s, respectively 1H), 8.06 (1H, dd), 8.70 ~ 9.18 (3H, m))

EXAMPLE 45

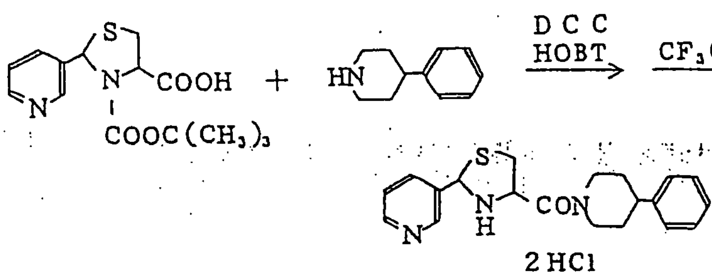


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and N-methyl-N-phenylhydrazine were used as the starting materials and treated in the same manner as in Example 43 to give N'-methyl-N'-phenyl-2-(3-pyridyl)thiazolidine-4-carbohydrazine dihydrochloride. Yield, 58%. Melting point 145°C.

NMR (DMSO-d_6)

δ: 3.04~3.72 (5H, m), 4.28~4.50 (1H, m), 6.03 and 6.12 (s, respectively 1H), 6.70~7.32 (5H, m), 8.07 (1H, dd), 8.69~9.17 (3H, m)

EXAMPLE 46

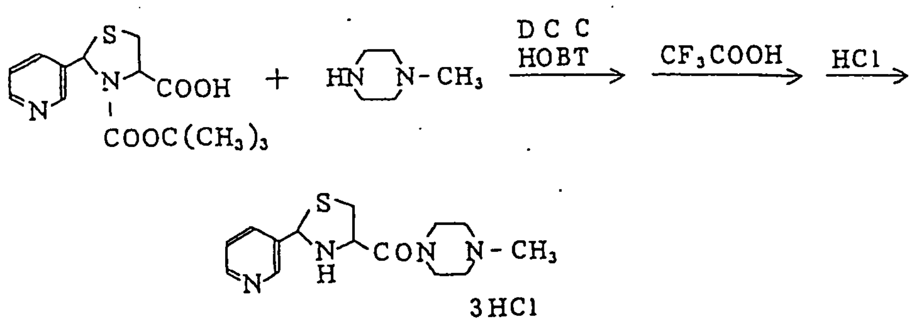


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and 4-phenylpiperidine were used as the starting materials and treated in the same manner as in Example 43 to give 4-phenyl-1-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperidine dihydrochloride. Yield, 48%. Melting point 115°C.

NMR (DMSO-d_6)

δ: 1.32~2.08 (4H, m), 2.58~3.82 (6H, m), 3.96~5.00 (2H, m), 6.04 and 6.28 (s, respectively 1H), 7.08~7.44 (5H, m), 8.06 (1H, dd), 8.68~9.16 (3H, m)

EXAMPLE 47



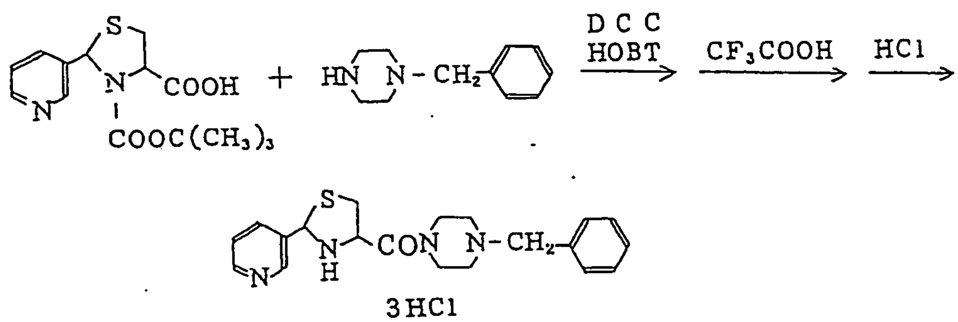
N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and 1-methylpiperazine were used as the

starting materials and treated in the same manner as in Example 43 to give 1-methyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride. Melting point 182°C.

NMR (DMSO-d_6)

δ: 2.62~5.00 (14H, m), 6.03 and 6.22 (s, respectively 1H), 8.09 (1H, dd), 8.70~9.20 (3H, m)

EXAMPLE 48

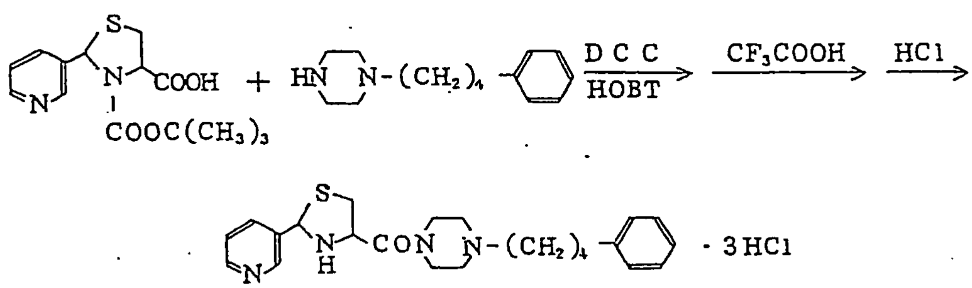


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and 1-benzylpiperazine were used as the starting materials and treated in the same manner as in Example 43 to give 1-benzyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride. Yield, 63%. Melting point 165°C.

NMR (DMSO-d_6)

δ: 2.76~4.80 (13H, m), 5.93 and 6.15 (s, respectively 1H), 7.36~7.80 (5H, m), 8.03 (1H, dd), 8.62~9.10 (3H, m)

EXAMPLE 49

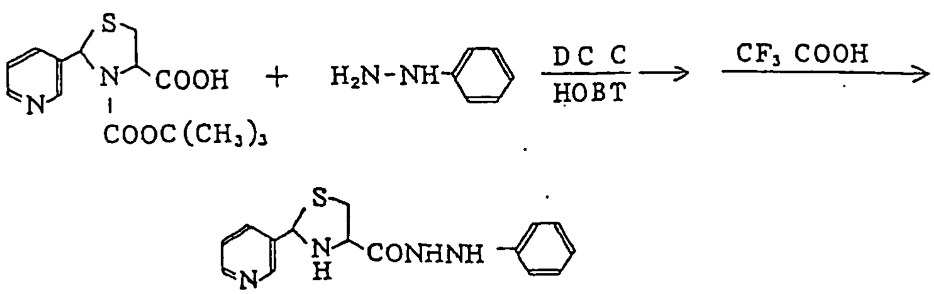


N-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid and 1-(4-phenylbutyl)piperazine were used as the starting materials and treated in the same manner as in Example 43 to give 1-(4-phenylbutyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride. Yield, 98%. Melting point 157°C.

NMR (DMSO-d_6)

δ: 1.33~1.85 (4H, m), 2.30~2.76 (8H, m), 2.86~3.78 (6H, m), 3.99~4.30 (1H, m), 5.96 and 6.17 (s, respectively 1H), 7.12~7.44 (6H, m), 8.12 (1H, dd), 8.72~9.17 (2H, m)

EXAMPLE 50

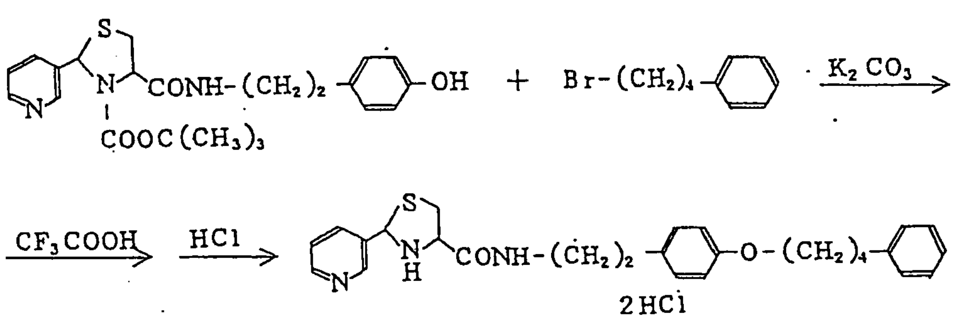


A solution of 450 mg of dicyclohexylcarbodiimide in 5 ml of tetrahydrofuran was added dropwise to a mixture of 680 mg of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid, 240 mg of phenylhydrazine, 450 mg of 1-hydroxybenzotriazole and 20 ml of tetrahydrofuran with ice cooling, and the resultant mixture was stirred with ice cooling for 1 hour and then at room temperature for 12 hours. The reaction mixture was diluted with 30 ml of ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave 840 mg of N'-phenyl-3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4 carbohydrazide. Trifluoroacetic acid (5 ml) was added to the thus-obtained compound, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave crystals, which were recrystallized from ethyl acetate. Thus was obtained 180 mg of N'-phenyl-2-(3-pyridyl)thiazolidine-4-carbohydrazide. Melting point 155°C.

NMR ($CDCl_3$ + DMSO-d_6)

δ: 3.22~3.56 (2H, m), 4.22~4.36 (1H, m), 5.60 and 5.72 (s, respectively 1H), 6.72~7.44 (6H, m), 7.81~7.95 (1H, m), 8.56 (1H, dd), 8.79 (1H, d)

EXAMPLE 51



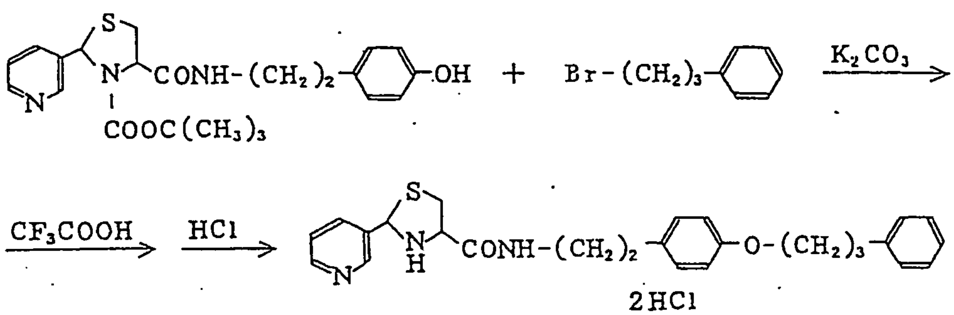
A solution of 280 mg of 1-bromo-4-phenylbutane in 5 ml of N,N-dimethylformamide was added to a mixture of 540 mg of N-[2-(p-hydroxyphenyl)ethyl]-3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxamide, 180 mg of potassium carbonate and 10 ml of N,N-dimethylformamide at room temperature. The mixture was stirred at 80°C for 3 days. After cooling, 20 ml of water was added to the reaction mixture, and the organic matter was extracted with ethyl acetate. The organic layer was washed in sequence with water and saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (eluent: hexane-ethyl acetate = 1:3) gave 360 mg of N-[2-[p-(4-phenylbutoxy)phenyl]ethyl]-3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxamide. Trifluoroacetic acid (5 ml) was added to the compound obtained, and the mixture was stirred at room temperature for 1.5 hour. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate and saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate) to give 230 mg of N-[2-[p-(4-phenylbutoxy)phenyl]ethyl]-2-(3 pyridyl)thiazolidine-4-carboxamide. This compound was dissolved in ethyl acetate, and 1 ml of 2 N hydrogen chloride solution in dioxane was added. The resultant solid was collected by filtration, washed with ethyl

acetate and dried to give 130 mg of N-[2-[p-(4-phenylbutoxy)phenyl]ethyl]-2-(3-pyridyl) thiazolidine-4-carboxamide dihydrochloride. Melting point 102°C.

Elemental analysis (for $C_{27}H_{33}N_3O_2SCl_2$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	60.67	6.22	7.86	6.00
Found:	60.51	6.15	7.94	5.97

EXAMPLE 52

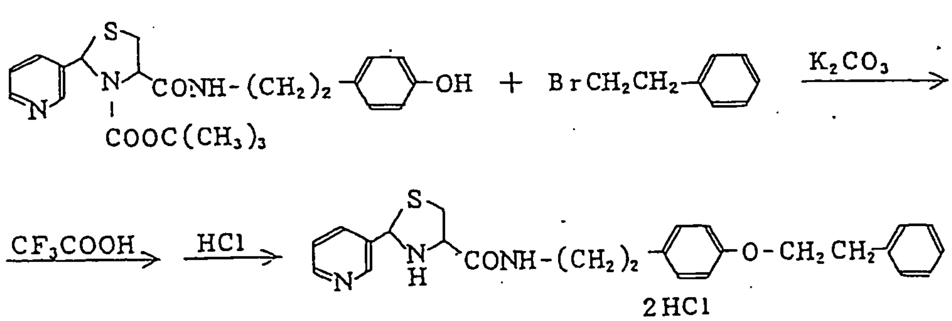


N-[2-(p-Hydroxyphenyl)ethyl]-3-tert-butoxycarbon-yl-2-(3-pyridyl)thiazolidine-4-carboxamide and 1-bromo-3-phenylpropane were used as the starting materials and treated in the same manner as in Example 51 to give N-[2-[p-(3-phenylpropoxy)phenyl]ethyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Melting point 98°C.

Elemental analysis (for $C_{26}H_{31}N_3O_2SCl_2 \cdot 0.3H_2O$)):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	59.38	6.06	7.99	6.10	13.48
Found:	59.37	6.05	8.01	6.09	13.31

EXAMPLE 53



N-[2-(p-Hydroxyphenyl)ethyl]-3-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxamide and 1-bromo-2-phenylethane were used as the starting materials and treated in the same manner as in Example 51 to give

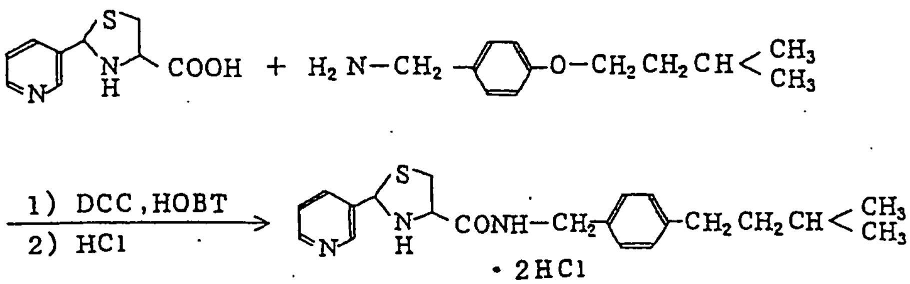
N-[2-[p-(2-phenylethoxy)phenyl]ethyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride.

NMR (DMSO-d_6)

δ: 2.58~3.64 (8H, m), 4.11~4.40 (3H, m), 6.03 (1H, s), 6.83~7.35 (5H, m), 8.02 (1H, dd), 8.66~8.85 (1H, m), 8.88~9.01 (1H, m), 9.07 (1H, dd)

MS: m/z 433 (M^+-2 x HCl)

EXAMPLE 54



A mixture of 1.13 g of p-(3-methylbutoxy)benzylamine, 1.29 g of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 1.25 g of dicyclohexylcarbodiimide and 0.82 g of 1-hydroxybenzotriazole in 20 ml of N,N-dimethylformamide was stirred overnight at room temperature. The reaction mixture was diluted with 100 ml of ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification of the thus-obtained residue by silica gel column chromatography (eluent: ethyl acetate) gave 2.20 g of N-[p-(3-methylbutoxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide. To a solution of this compound in 60 ml of ethyl acetate was added 4 ml of 4 N hydrogen chloride solution in dioxane. The precipitate solid was collected by filtration, washed with ethyl acetate and dried under reduced pressure to give 2.30 g of N-[p-(3-methylbutoxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride. Melting point 120-128°C.

Elemental analysis (for $C_{21}H_{29}N_3O_2SCl_2 \cdot 0.4H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	54.17	6.45	9.02	6.89	15.23
Found:	54.23	6.37	8.96	7.00	15.16

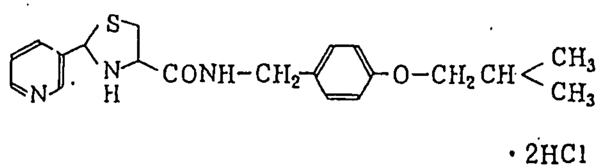
EXAMPLES 55 TO 80

The following compounds were obtained in the same manner as in Example 54.

Desired Product

Chemical Structure and Chemical Name

Ex. 55



N-[p-2-Methylpropoxy)benzyl]-2-(3-pyridyl)thiazolidine-3-carboxamide dihydrochloride

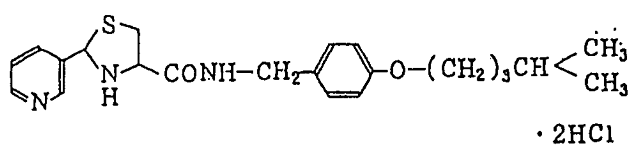
Physicochemical Properties

1) Melting point: 125~133°C

2) Elemental analysis (for $C_{20}H_{27}N_3O_2SCl_2$):

	C	H	N	S
Calculated: (%)	54.05	6.12	9.45	7.22
Found: (%)	53.69	6.19	9.32	6.97

Ex. 56



N-[p-(4-Methylpentyloxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

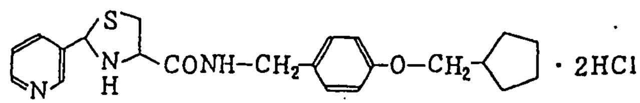
Physicochemical Properties

1) Melting point: 124~128°C

2) Elemental analysis (for $C_{22}H_{31}N_3O_2SCl_2$):

	C	H	N	S	Cl
Calculated: (%)	54.88	6.70	8.73	6.66	14.73
Found: (%)	54.79	6.69	8.70	6.48	14.80

Ex. 57



N-(p-Cyclopentylmethoxybenzyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

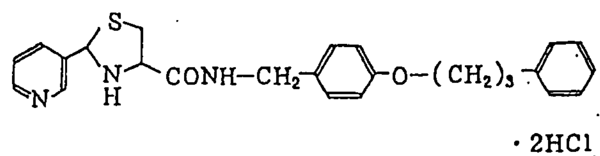
Physicochemical Properties

1) Melting point: 55~60°C

2) Elemental analysis (for $C_{22}H_{20}N_3O_2SCl_2$):

	C	H	N	S
Calculated: (%)	56.17	6.21	8.93	6.82
Found: (%)	55.83	6.11	8.65	6.84

Ex. 58



N-[p-(3-Phenylpropoxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

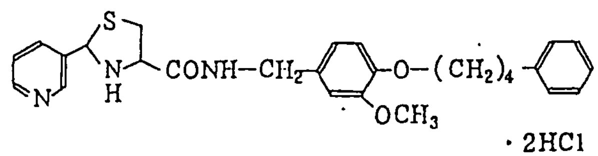
Physicochemical Properties

1) Melting point: 110~116°C

2) Elemental analysis (for $C_{25}H_{20}N_3O_2SCl_2$):

	C	H	N	S	Cl
Calculated: (%)	59.28	5.77	8.30	6.33	14.00
Found: (%)	58.95	5.74	8.21	6.36	13.93

Ex. 59



N-[3-Methoxy-4-(4-phenylbutoxy)-benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

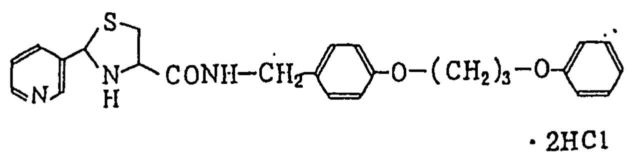
Physicochemical Properties

1) Melting point: 88~95°C

2) Elemental analysis (for $C_{27}H_{33}N_3O_3SCl_2$):

	C	H	N	S	Cl
Calculated: (%)	58.90	6.04	7.63	5.82	12.88
Found: (%)	58.52	6.02	7.59	5.82	12.48

Ex. 60



N-[p-(3-Phenoxypropoxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

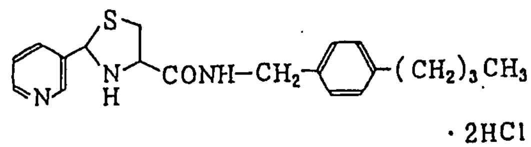
Physicochemical Properties

1) Melting point: 101~110°C

2) Elemental analysis (for $C_{25}H_{29}N_3O_3SCl_2$):

	C	H	N	S	Cl
Calculated: (%)	57.47	5.59	8.04	6.14	13.57
Found: (%)	57.42	5.77	7.90	5.98	13.35

Ex. 61



N-(p-Butylbenzyl)-2-(3-pyridyl)-thiazolidine-4-carboxamide dihydrochloride

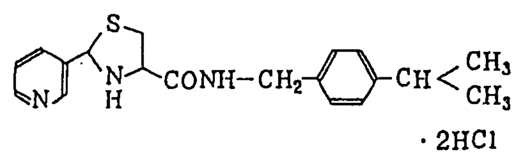
Physicochemical Properties

1) Melting point: 110~115°C

2) Elemental analysis
(for $C_{20}H_{27}N_3OSCl_2 \cdot 0.4H_2O$):

	C	H	N	S	Cl
Calculated: (%)	55.14	6.43	9.65	7.36	16.28
Found: (%)	55.27	6.50	9.69	7.23	16.06

Ex. 62



N-[p-(1-Methylethyl)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

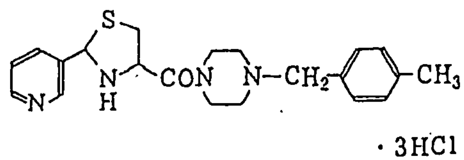
Physicochemical Properties

1) Melting point: 133~142°C

2) Elemental analysis
(for $C_{19}H_{25}N_3OSCl_2 \cdot 0.6H_2O$):

	C	H	N	S	Cl
Calculated: (%)	53.67	6.21	9.88	7.54	16.68
Found: (%)	53.75	6.17	9.83	7.52	16.37

Ex. 63



1-(p-Methylbenzyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

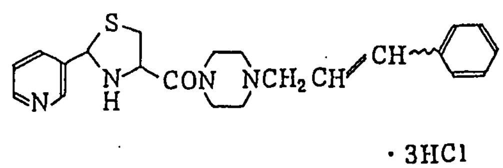
Physicochemical Properties

1) Melting point: 168°C

2) NMR ($DMSO-d_6$)

δ: 2.38 (3H, s), 2.5~3.5 (8H, m), 4.0~4.6 (4H, m), 4.4~4.9 (1H, m), 5.96 and 6.18 (s, respectively 1H), 7.26 and 7.56 (4H, dd, ABq), 6.9~7.2 (1H, m), 7.6~8.2 (3H, m)

Ex. 64



1-(3-Phenyl-2-propenyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperazine trihydrochloride

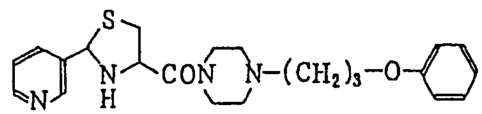
Physicochemical Properties

1) Melting point: 180°C

2) NMR ($DMSO-d_6$)

δ: 2.38~3.8 (8H, m), 3.8~4.1 (2H, m), 4.0~4.8 (3H, m), 5.98 and 6.18 (s, respectively 1H), 6.3~6.7 (1H, m), 6.8 and 6.86 (s, respectively 1H), 7.2~7.6 (5H, m), 8.0~8.2 (1H, m), 8.6~9.2 (3H, m)

Ex. 65



· 3HCl

1-(3-Phenoxypropyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperazine trihydrochloride

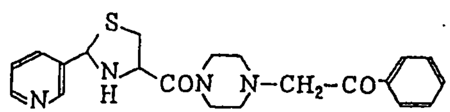
Physicochemical Properties

1) MS: m/z 412 (M^+-3HCl)

2) NMR (DMSO-d_6)

δ: 2.0~2.6 (2H, m), 2.6~3.9 (10H, m), 4.09 (2H, t), 4.0~4.9 (3H, m), 6.0 and 6.2 (s, respectively 1H), 6.8~7.1 (3H, m), 6.2~6.42 (2H, m), 8.0~8.2 (1H, m), 8.6~9.2 (3H, m)

Ex. 66



· 3HCl

1-[(2-Oxo-2-phenyl)ethyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperazine trihydrochloride

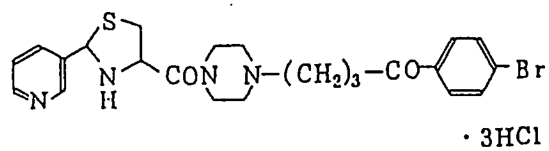
Physicochemical Properties

1) Melting point: 147°C

2) NMR (DMSO-d_6)

δ: 2.94~4.32 (12H, m), 4.52~4.80 (1H, m), 5.96 and 6.16 (s, respectively 1H), 7.44~7.84 (3H, m), 7.94~8.20 (3H, m), 8.60~9.20 (3H, m)

Ex. 67



1-[4-(p-Bromophenyl)-4-oxobutyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

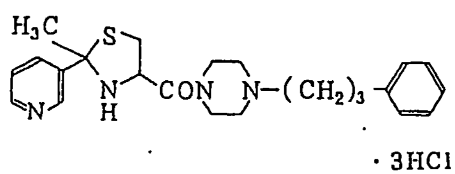
Physicochemical Properties

1) Melting point: 139°C

2) Elemental analysis (for $C_{23}H_{30}N_4O_2SBrCl_3$):

	C	H	N	S	Br+Cl
Calculated: (%)	45.08	4.93	9.14	5.23	30.39
Found: (%)	44.90	5.17	9.24	5.41	30.29

Ex. 68



1-[2-Methyl-2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine trihydrochloride

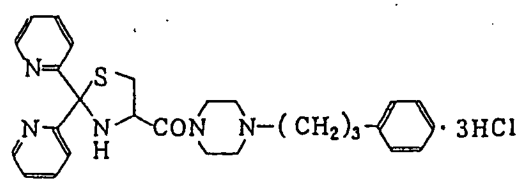
Physicochemical Properties

1) Melting point: 129°C

2) NMR (DMSO-d_6)

δ: 1.88 and 1.96 (s, respectively 3H), 1.68~2.28 (2H, m), 2.44~2.80 (2H, m), 2.88~4.64 (13H, m), 7.12~7.48 (6H, m), 7.96~8.18 (1H, m), 8.64~9.04 (2H, m)

Ex. 69



1-[2,2-Di(2-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)-piperazine trihydrochloride

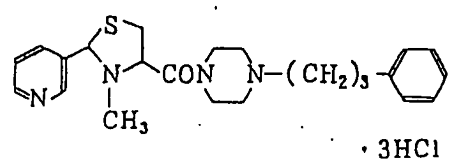
Physicochemical Properties

1) Melting point: 111°C

2) NMR (DMSO-d_6)

δ: 1.90~2.28 (2H, m), 2.46~2.80 (2H, m), 2.86~3.74 (12H, m), 4.12~4.68 (1H, m), 7.16~7.40 (5H, m), 7.44~8.88 (8H, m)

Ex. 70



1-[3-Methyl-2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenyl-propyl)piperazine trihydrochloride

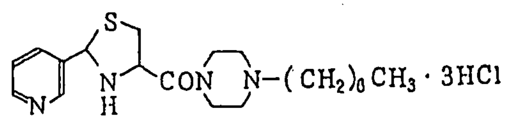
Physicochemical Properties

1) Melting point: 130°C

2) NMR (DMSO-d_6)

δ: 1.88~2.24 (2H, m), 2.36 and 2.52 (s, resepectively 3H), 2.56~2.78 (2H, m), 2.78~4.60 (13H, m), 5.58 and 5.82 (s, respesctively 1H), 7.08~7.44 (6H, m), 7.86~8.20 (1H, m), 8.58~9.02 (2H, m)

Ex. 71



1-Heptyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

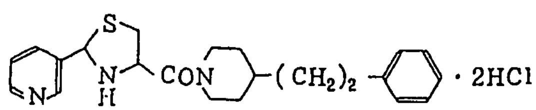
Physicochemical Properties

1) Melting point: 139°C

2) Elemental analysis
(for $C_{20}H_{35}N_4OSCl_3 \cdot 1.5H_2O$):

	C	H	N	S	Cl
Calculated: (%)	46.83	7.47	10.92	6.25	20.73
Found: (%)	47.09	7.29	11.09	6.36	20.47

Ex. 72



4-(2-Phenylethyl)-1-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperidine dihydrochloride

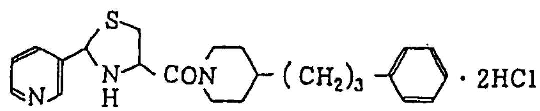
Physicochemical Properties

1) Melting point: 110~117°C

2) Elemental analysis
(for $C_{22}H_{29}N_3OSCl_2 \cdot 0.8H_2O$):

	C	H	N	S	Cl
Calculated: (%)	56.36	6.58	8.96	6.84	15.12
Found: (%)	56.27	6.55	8.92	6.94	15.02

Ex. 73



4-(3-Phenylpropyl)-1-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperidine dihydrochloride

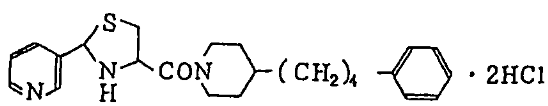
Physicochemical Properties

1) Melting point: 104~112°C

2) Elemental analysis
(for $C_{23}H_{31}N_3OSCl_2 \cdot 0.4H_2O$):

	C	H	N	S	Cl
Calculated: (%)	58.07	6.74	8.83	6.74	14.91
Found: (%)	58.03	6.64	8.80	6.81	14.96

Ex. 74



4-(4-Phenylbutyl)-1-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperidine dihydrochloride

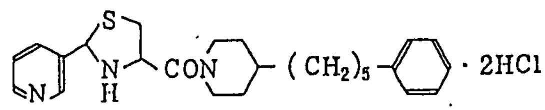
Physicochemical Properties

1) Melting point: 108~116°C

2) Elemental analysis
(for $C_{24}H_{33}N_3OSCl_2 \cdot 0.8H_2O$):

	C	H	N	S	Cl
Calculated: (%)	58.01	7.02	8.46	6.45	14.27
Found: (%)	57.89	6.77	8.43	6.59	14.42

Ex. 75



4-(5-Phenylpentyl)-1-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperidine dihydrochloride

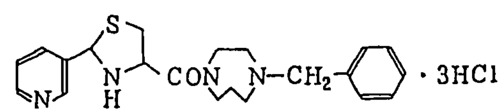
Physicochemical Properties

Melting point: 110~118°C

Elemental analysis
(for $C_{25}H_{33}N_3OSCl_2 \cdot 0.5H_2O$):

	C	H	N	S	Cl
Calculated: (%)	59.40	7.18	8.31	6.36	14.03
Found: (%)	59.56	7.21	8.36	6.47	13.89

Ex. 76



4-Benzyl-1-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]homopiperazine trihydrochloride

Physicochemical Properties

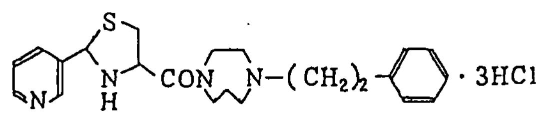
1) Melting point: 168~175°C

2) NMR (DMSO-d_6)

δ: 1.80~2.50 (2H, m), 2.82~3.86 (8H, m), 3.86~4.73 (3H, m), 4.36 (2H, brs), 5.50~6.45 (3H, br), 5.94 and 6.16 (s, respectively 1H), 7.35~7.57 (3H, m), 7.57~7.81 (2H, m), 7.92~8.17 (1H, m), 8.57~9.14 (3H, m), 11.08~11.60 (1H, br)

3) MS: m/z 382 (M^+-3HCl)

Ex. 77



4-(2-Phenylethyl)-1-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]homopiperazine trihydrochloride

Physicochemical Properties

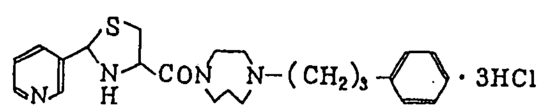
1) Melting point: 161~169°C

2) NMR (DMSO-d_6)

δ: 1.91~2.45 (2H, m), 2.95~4.34 (14H, m), 4.45~4.92 (1H, br), 6.02 and 6.21 (s, respectively 1H), 6.40~7.09 (3H, br), 7.31 (5H, s), 7.95~8.20 (1H, m), 8.67~9.22 (3H, m), 11.36~11.87 (1H, br)

3) MS: m/z 396 (M^+-3HCl)

Ex. 78



4-(3-Phenylpropyl)-1-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]homopiperazine trihydrochloride

Physicochemical Properties

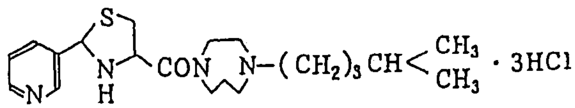
1) Melting point: 162~170°C

2) NMR (DMSO-d_6)

δ: 1.79~2.30 (4H, m), 2.64 (2H, t, J=7Hz), 2.85~4.31 (12H, m), 4.36~4.75 (1H, br), 5.25~6.10 (3H, br), 5.94 and 6.16 (s, respectively 1H), 7.29 (5H, s), 7.92~8.16 (1H, m), 8.59~9.15 (3H, m), 11.15~11.60 (1H, br)

3) MS: m/z 410 (M^+-3HCl)

Ex. 79



4-(4-Methylpentyl)-1-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]homopiperazine trihydrochloride

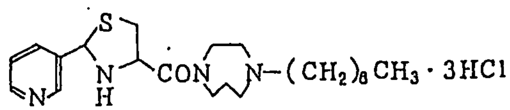
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 0.87 (6H, d, J=7Hz), 1.02~1.30 (2H, m), 1.39~2.42 (3H, m), 2.82~4.28 (14H, m), 4.50~4.93 (1H, br), 6.03 and 6.21 (s, respectively 1H), 6.11~6.90 (3H, br), 7.96~8.22 (1H, m), 8.66~9.20 (3H, m), 10.95~11.40 (1H, br)

2) MS: m/z 376 (M^+-3HCl)

Ex. 80



4-Heptyl-1-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]homopiperazine trihydrochloride

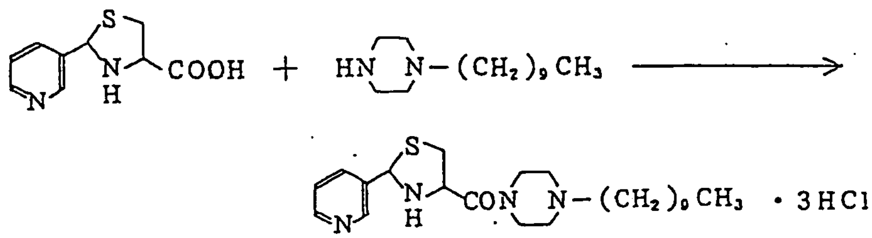
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 0.87 (3H, t, J=6Hz), 1.08~1.46 (8H, br s), 1.54~1.89 (2H, m), 2.04~2.61 (2H, m), 2.83~4.36 (14H, m), 4.52~4.96 (1H, m), 6.05 and 6.24 (s, respectively 1H), 7.97~8.23 (1H, m), 8.67~9.60 (6H, m), 11.20~11.65 (1H, br)

2) MS: m/z 390 (M^+-3HCl)

EXAMPLE 81



Dicyclohexylcarbodiimide (0.34 g) was added to a mixture of 0.34 g of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 0.37 g of 1-decylpiperazine, 0.33 g of 1-hydroxybenzotriazole and 10 ml of N,N-dimethylformamide with ice cooling, and the resultant mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed with saturated aqueous solution of sodium hydrogen carbonate and then with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Ethyl acetate (5 ml) was added to the residue, and the insoluble matter was filtered of. 2 N Hydrogen chloride solution in dioxane was added to the filtrate. The resultant crystals were collected by filtration, washed with ethyl acetate and dried to give 0.63 g of 1-decyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride. Melting point 170°C.

Elemental analysis (for $C_{23}H_{41}N_4OSCl_3 \cdot H_2O$):

	C (%)	H (%)	N (%)	S (%)	Cl (%)
Calculated:	50.59	7.94	10.26	5.87	19.48
Found:	50.50	7.81	10.22	6.07	19.47

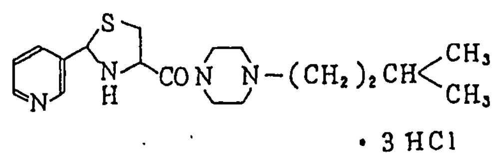
EXAMPLES 82 TO 85

The following compounds were obtained in the same manner as in Example 81.

Desired Product

Chemical Structure and Chemical Name

Ex. 82



1-(3-Methylbutyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

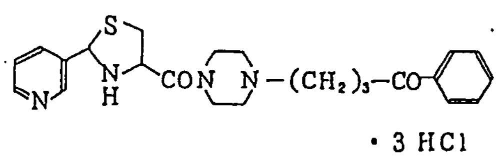
Physicochemical Properties

1) Melting point: 153°C

2) Elemental analysis
(for $C_{18}H_{31}N_4OSCl_3 \cdot 1.7H_2O$):

	C	H	N	S	Cl
Calculated: (%)	44.26	7.10	11.47	6.56	21.77
Found: (%)	44.28	6.97	11.47	6.74	21.57

Ex. 83



1-(4-Oxo-4-phenylbutyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperazine trihydrochloride

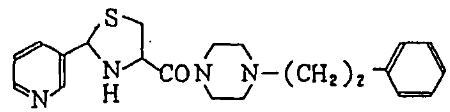
Physicochemical Properties

1) Melting point: 145°C

2) Elemental analysis
(for $C_{23}H_{30}N_4O_2SCl_3 \cdot {}^3/_2H_2O$):

	C	H	N	S	Cl
Calculated: (%)	49.25	6.11	9.99	5.72	18.96
Found: (%)	49.40	5.97	9.79	5.92	18.81

Ex. 84



• 3 HCl

1-(2-Phenylethyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

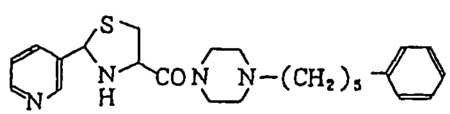
Physicochemical Properties

1) Melting point: 155°C

2) lemental analysis
(for $C_{21}H_{28}N_4OSCl_3 \cdot {}^2/_5H_2O$):

	C	H	N	S
Calculated: (%)	50.64	5.83	11.25	6.44
Found: (%)	50.74	6.11	11.21	6.44

Ex. 85



• 3 HCl

1-(5-Phenylpentyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

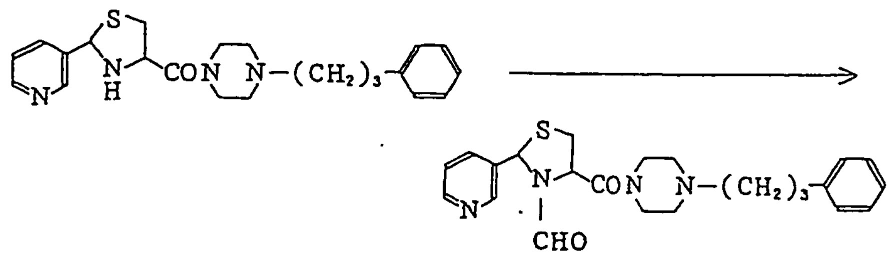
Physicochemical Properties

1) Melting point: 136°C

2) Elemental analysis (for $C_{24}H_{35}N_4OSCl_3 \cdot H_2O$):

	C	H	N	S	Cl
Calculated: (%)	52.22	6.76	10.15	5.81	19.27
Found: (%)	51.98	6.71	10.12	5.93	19.46

EXAMPLE 86



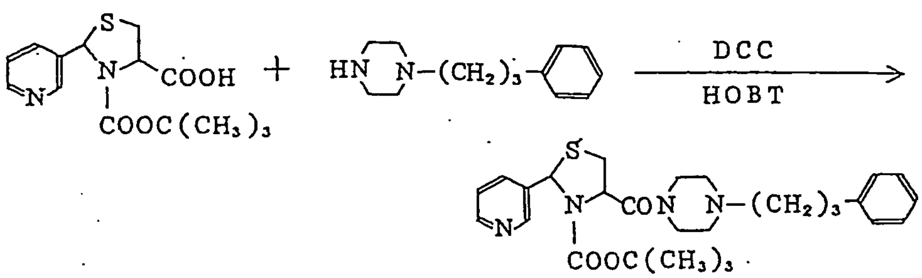
To a solution of 40 mg of 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine in 5 ml of dichloromethane, there was added 0.5 ml of a formic acid-acetic anhydride (5:3, v/v) mixture, and the resultant mixture was stirred overnight at room temperature. Ethyl acetate (20 ml) was added to the reaction mixture, the dilution was washed with 5% aqueous sodium hydrogen carbonate and with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 30 mg of 1-[3-formyl-2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine as an oil.

NMR ($CDCl_3$)

δ: 1.6~2.0 (2H, m), 2.2~2.8 (8H, m), 3.0~3.4 (2H, m), 3.6~3.9 (4H, m), 5.0~5.7 (1H, m), 6.14 and 6.4 (s, respectively 1H), 7.0~7.5 (5H, m), 7.6~7.9 (1H, m), 8.24 (1H, s), 8.4~8.8 (3H, m)

MS: m/z 424 (M^+)

EXAMPLE 87



3-tert-Butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid (650 mg) and 1-(3-phenylpropyl)piperazine (400 mg) were used as the starting materials and treated in the same manner as in Example 54. Without conversion to the hydrochloride, the product was purified by silica gel column chromatography (eluent: ethyl acetate). Thus was obtained 1-[3-(tert-butoxycarbonyl)-2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine (560 mg) as an oil.

NMR ($CDCl_3$)

δ: 1.40 (9H, s), 1.6~2.1 (2H, m), 2.2~2.8 (8H, m), 3.0~3.4 (2H, m), 3.4~4.0 (6H, m), 5.08 (1H, br t), 6.16 (1H, br s), 7.0~7.5 (5H, m), 8.4~8.8 (4H, m)

MS: m/z 496 (M^+)

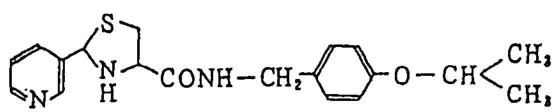
EXAMPLES 88 AND 89

The following compounds were obtained in the same manner as in Example 87.

Desired Product

Chemical Structure and Chemical Name

Ex. 88



N-[p-(2-Methylethoxy)benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide

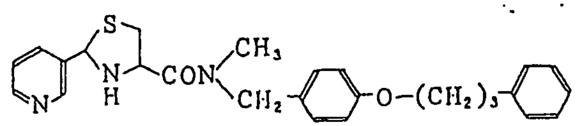
Physicochemical Properties

1) MS: m/z 357 (M^+)

2) NMR ($CDCl_3$)

δ: 1.34 (6H, d, J=7Hz), 2,5 (1H, br, exchange with D_2O), 3.38 (1H, dd, J=13, 8Hz), 3.73 (1H, dd, J=13, 5Hz), 3.98 and 4.40 (m, respectively 1H), 4.3~4.6 (3H), 5.40 and 5.60 (s, respectively 1H), 6.8~6.9 (2H), 7.1~7.4 (3H), 7.4 (1H, br, exchange with D_2O), 7.80 (1H, m), 8.54 (1H, m), 8.68 (1H, m)

Ex. 89



N-Methyl-N-[p-(3-phenylpropoxy)-benzyl]-2-(3-pyridyl)thiazolidine-4-carboxamide

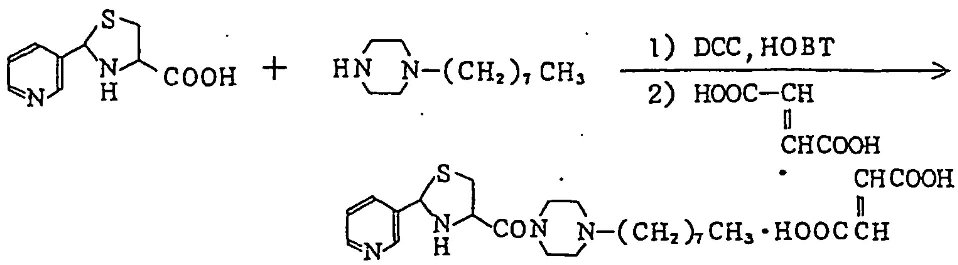
Physicochemical Properties

1) MS: m/z : 447 (M^+)

2) NMR ($CDCl_3$)

δ: 2.0~2.3 (2H), 2.6~3.5 (5H), 3.01 and 3.03 (s, respectively 3H), 3.96 (2H, t, J=7Hz), 3.9~4.1 (1H), 4.6 (2H, br s), 5.58 and 5.98 (s, respectively 1H), 6.8~7.4 (10H), 7.7~8.0 (1H), 8.4~8.7 (1H), 8.75 (1H, br s)

EXAMPLE 90



Dicyclohexylcarbodiimide (0.82 g) was added to a mixture of 0.84 g of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 0.79 g of 1-octylpiperazine, 0.54 g of 1-hydroxybenzotriazole and 20 ml of N,N-dimethylformamide with ice cooling, and the resultant mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, and the insoluble matter was filtered off. The filtrate was washed in sequence with saturated aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure. Ethyl acetate was added to the residue, the insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol-ethyl acetate), the oil obtained was dissolved in 25 ml of ethanol, and 0.32 g of fumaric acid was added. After allowing the mixture to stand for 2 days, the resultant crystals were collected by filtration, washed with cold ethanol and dried. Thus was obtained 0.72 g of 1-octyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate. Melting point 135°C.

Elemental analysis (for $C_{25}H_{38}N_4O_6S$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	59.27	7.56	11.06	6.33
Found:	59.01	7.66	10.95	6.27

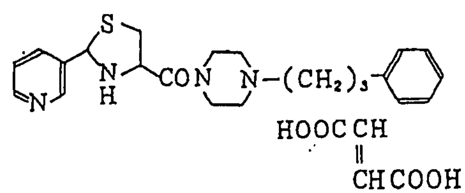
EXAMPLES 91 TO 94

The following compounds were obtained in the same manner as in Example 90.

Desired Product

Chemical Structure and Chemical Name

Ex. 91



1-(3-Phenylpropyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine fumarate

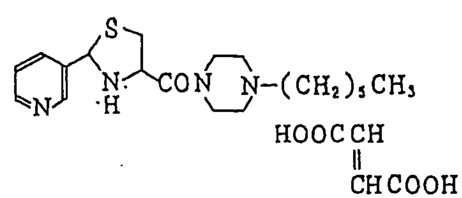
Physicochemical Properties

1) Melting point: 175°C

2) Elemental analysis (for $C_{26}H_{32}N_4O_5S$):

	C	H	N	S
Calculated: (%)	60.92	6.29	10.93	6.26
Found: (%)	60.62	6.25	10.79	6.17

Ex. 92



1-Hexyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

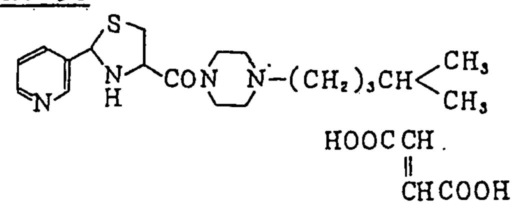
Physicochemical Properties

1) Melting point: 128°C

2) Elemental analysis (for $C_{23}H_{34}N_4O_5S$):

	C	H	N	S
Calculated: (%)	57.72	7.16	11.71	6.70
Found: (%)	57.60	7.22	11.61	6.60

Ex. 93



1-(4-Methylpentyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine fumarate

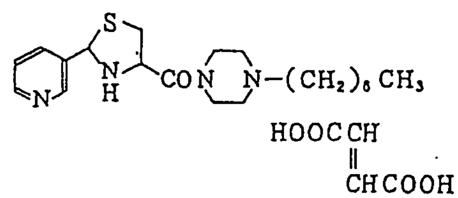
Physicochemical Properties

1) Melting point: 148°C

2) Elemental analysis (for $C_{23}H_{34}N_4O_5S$):

	S
Calculated (%):	6.70
Found (%):	6.78

Ex. 94



1-Heptyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

Physicochemical Properties

1) Melting point: 153°C

2) Elemental analysis (for $C_{24}H_{36}N_4O_5S$):

	C	H	N	S
Calculated: (%)	58.51	7.37	11.37	6.51
Found: (%)	58.46	7.38	11.28	6.63

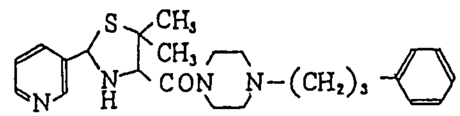
EXAMPLES 95 TO 131

The following compounds of Examples 95 to 105, compounds of Examples 106 to 116, and compounds of Examples 117 to 131 were obtained in the same manner as in Examples 54, 87 and 90, respectively.

Desired Product

Chemical Structure and Chemical Name

Ex. 95



• 3 HCl

1-[5,5-Dimethyl-2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine trihydrochloride

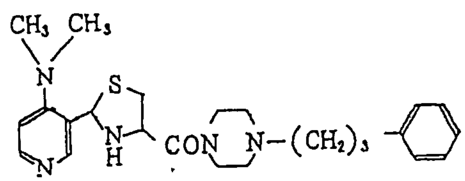
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.22~1.80 (6H, m), 1.92~2.28 (1H, m), 2.44~2.80 (2H, m), 2.84~4.88 (11H, m), 6.00~6.18 (1H), 7.12~7.48 (5H, m), 7.92~8.12 (1H, m), 8.52~8.72 (1H, m), 8.78~9.04 (2H, m)

2) MS: (FAB) m/z 452 (M^{+}+1-3HCl)

Ex. 96



• 3 HCl

1-[2-(4-Dimethylamino-3-pyridyl)-thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine trihydrochloride

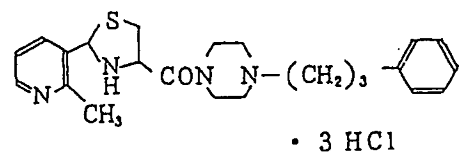
Physicochemical Properties

1) Melting point: 143~145°C

2) Elemental analysis (for $C_{24}H_{36}N_5OSCl_3 \cdot 2H_2O$):

	C	H	N	S	Cl
Calculated: (%)	49.27	6.89	11.97	5.48	18.18
Found: (%)	49.35	6.50	11.56	5.65	17.91

Ex. 97



1-[2-(2-Methyl-3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)-piperazine trihydrochloride

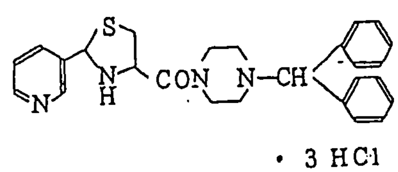
Physicochemical Properties

1) Melting point: 138~140°C

2) Elemental analysis (for $C_{23}H_{33}N_4OSCl_3$):

	C	H	N	S
Calculated: (%)	49.69	6.71	10.08	5.77
Found: (%)	49.78	6.51	9.97	5.74

Ex. 98



1-Benzhydryl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride

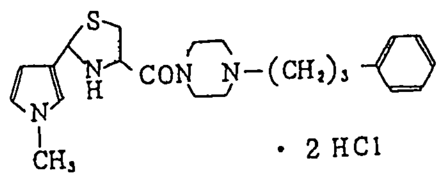
Physicochemical Properties

1) Melting point: 173~174°C

2) Elemental analysis (for $C_{26}H_{31}N_4O_2SCl_3 \cdot 1.8H_2O$):

	C	H	N	S
Calculated: (%)	53.25	5.95	9.55	5.47
Found: (%)	53.41	5.83	9.48	5.27

Ex. 99



· 2 HCl

1-[2-(1-Methyl-3-pyrrolyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)-piperazine dihydrochloride

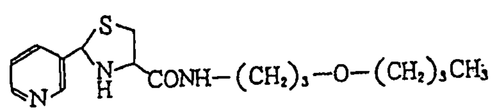
Physicochemical Properties

1) Melting point: 125°C

2) Elemental analysis (for $C_{22}H_{32}N_4OSCl_2 \cdot 1.5H_2O$):

	C	H	N	S	Cl
Calculated: (%)	53.01	7.08	11.24	6.43	14.22
Found: (%)	52.97	6.89	10.93	6.60	14.35

Ex. 100



· 2 HCl

N-(3-Butoxypropyl)-2-(3-pyridyl)-thiazolidine-4-carboxamide dihydrochloride

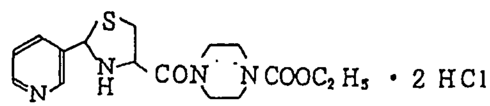
Physicochemical Properties

1) Melting point: 125~130°C

2) Elemental analysis (for $C_{16}H_{27}N_3O_2SCl_2$):

	C	H	N	S
Calculated: (%)	48.48	6.87	10.60	8.09
Found: (%)	48.18	6.85	10.26	8.17

Ex. 101



1-Ethoxycarbonyl-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine dihydrochloride

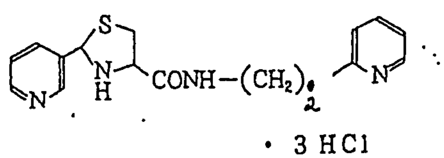
Physicochemical Properties

1) Melting point: 168°C

2) Elemental analysis (for $C_{16}H_{24}N_4O_3SCl_2$):

	C	H	N
Calculated: (%)	45.39	5.71	13.23
Found: (%)	45.12	5.52	13.02

Ex. 102



N-[2-(2-Pyridyl)ethyl]-2-(3-pyridyl)-thiazolidine-4-carboxamide trihydrochloride

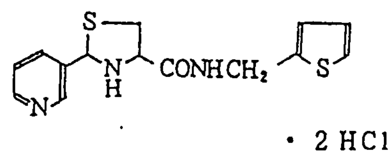
Physicochemical Properties

1) Melting point: 65~70°C

2) Elemental analysis (for $C_{16}H_{21}N_4OSCl_3 \cdot 1.6H_2O$):

	C	H	N	S	Cl
Calculated: (%)	42.46	5.39	12.38	7.08	23.50
Found: (%)	42.41	5.33	12.13	6.91	23.46

Ex. 103



N-(2-Thienylmethyl)-2-(3-pyridyl)-thiazolidine-4-carboxamide dihydrochloride

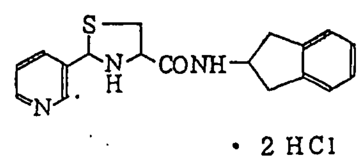
Physicochemical Properties

1) Melting point: 109~111°C

2) Elemental analysis (for $C_{14}H_{17}N_3OS_2Cl_2 \cdot 0.9H_2O$):

	C	H	N	S
Calculated: (%)	42.62	4.80	10.65	16.25
Found: (%)	42.80	4.77	10.74	16.00

Ex. 104



N-(2-Indanyl)-2-(3-pyridyl)thiazolidine-4-carboxamide dihydrochloride

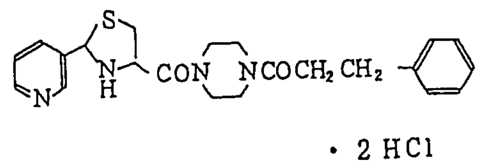
Physicochemical Properties

1) Melting point: 124~127°C

2) Elemental analysis (for $C_{18}H_{21}N_3OSCl_2$):

	C	H	N	S
Calculated: (%)	54.27	5.31	10.55	8.05
Found: (%)	54.11	5.36	10.31	7.95

Ex. 105



1-(3-Phenylpropionyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperazine dihydrochloride

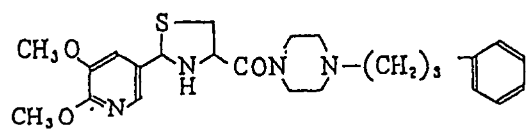
Physicochemical Properties

1) Melting point: 130°C

2) NMR (DMSO-d_6)

δ: 2.6~2.8 (4H, m), 3.3~3.8 (8H, m), 4.5~4.9 (1H, m), 5.98 and 6.20 (s, respectively 1H), 7.26 (5H, s), 7.9~8.2 (1H, m), 8.6~9.2 (3H, m)

Ex. 106



1-[2-(5,6-Dimethoxy-3-pyridyl)-thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine

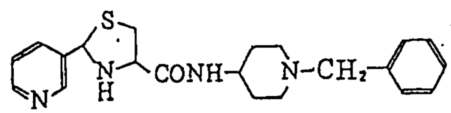
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.52~1.96 (2H, m), 2.18~2.72 (8H, m), 2.90~4.40 (13H, m), 5.40~5.84 (1H, m), 7.12~7.40 (5H, m), 7.40~7.50 (1H, m), 7.70~7.84 (1H, m)

2) MS: m/z 456 (M^+)

Ex. 107



N-(1-Benzyl-4-piperidinyl)-2-(3-pyridyl)thiazolidine-4-carboxamide

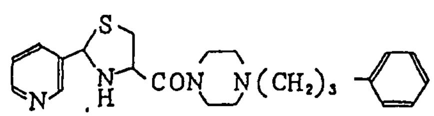
Physicochemical Properties

1) Melting point: 131~134°C

2) Elemental analysis (for $C_{21}H_{26}N_4OS$):

	C	H	N	S
Calculated: (%)	65.94	6.85	14.65	8.38
Found: (%)	65.69	6.83	14.46	8.43

Ex. 108



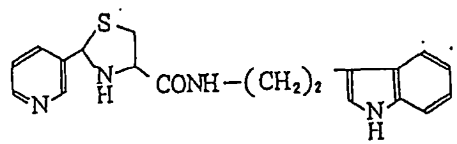
1-(3-Phenylpropyl)-4-[2-(3-pyridyl)-thiazolidin-4-ylcarbonyl]piperazine

Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.6~2.0 (2H, m), 2.2~3.8 (14H, m), 3.8~4.2 (1H, m), 5.62 and 5.98 (d, respectively 1H), 7.0~7.5 (6H, m), 7.7~8.0 (1H, m), 8.4~8.7 (1H, m), 8.7~8.9 (1H, m)

Ex. 109



N-[2-(3-Indolyl)ethyl]-2-(3-pyridyl)thiazolidine-4-carboxamide

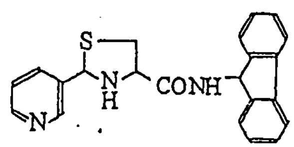
Physicochemical Properties

1) Melting point: 169~170°C

2) Elemental analysis (for $C_{19}H_{20}N_4OS$):

	C	H	N	S
Calculated: (%)	64.75	5.72	15.90	9.10
Found: (%)	64.52	5.67	15.70	9.07

Ex. 110



N-(9-Fluorenyl)-2-(3-pyridyl)-thiazolidine-4-carboxamide

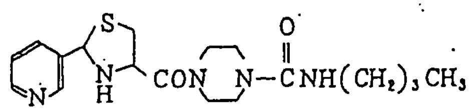
Physicochemical Properties

1) Melting point: 194~196°C

2) Elemental analysis (for $C_{22}H_{19}N_3OS$):

	C	H	N	S
Calculated: (%)	70.75	5.13	11.25	8.59
Found: (%)	70.51	5.16	10.99	8.51

Ex. 111



1-Butylaminocarbonyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine

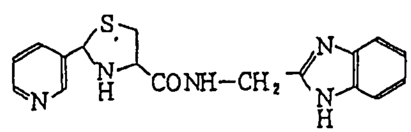
Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 0.94 (3H, t), 1.1~1.7 (4H, m), 3.0~3.8 (12H, m), 3.9~4.3 (1H, m), 5.58, and 5.94 (s, respectively 1H), 7.2~7.4 (1H, m), 7.7~8.0 (1H, m), 8.4~8.6 (1H, m), 8.6~8.8 (1H, m)

2) MS: m/z 378 (M^{+}+1)

Ex. 112



N-(2-Benzimidazolyl)methyl-2-(3-pyridyl)thiazolidine-4-carboxamide

Physicochemical Properties

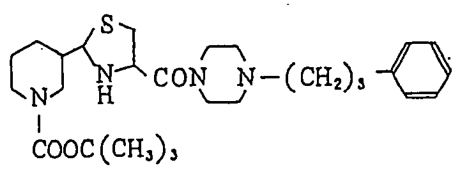
1) Melting point: 96~99°C

2) NMR ($CDCl_3$)

δ: 3.2~3.7 (2H), 4.3 (1H, m), 4.6~4.8 (2H), 5.5~5.6 (1H), 7.2~7.4 (3H), 7.5~7.6 (3H), 7.7~7.9 (1H), 8.4~8.6 (2H), 8.66 (1H, d, J=3Hz)

3) MS: m/z 339 (M^{+})

Ex. 113



1-[2-(1-tert-Butoxycarbonyl-3-piperidinyl)thiazolidin-4-yl-carbonyl]-4-(3-phenylpropyl)-piperazine

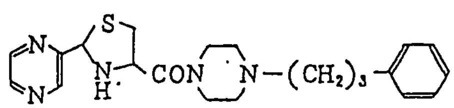
Physicochemical Properties

1) Elemental analysis (for $C_{27}H_{42}N_4O_3S$):

	C	H	N	S
Calculated: (%)	64.51	8.42	11.14	6.38
Found: (%)	64.21	8.45	10.83	6.38

2) MS: m/z 502 (M^+)

Ex. 114



1-(3-Phenylpropyl)-4-[2-(2-pyrazyl)thiazolidine-4-yl-carbonyl]piperazine

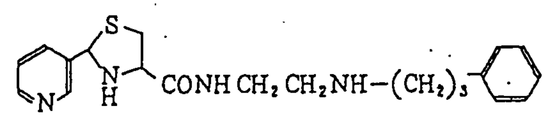
Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.6~2.0 (2H, m), 2.2~2.8 (8H, m), 3.0~3.4 (2H, m), 3.5~4.0 (4H, m), 4.0~4.2 (1H, m), 5.67 and 5.80 (s, respectively 1H), 7.1~7.3 (5H, m), 8.6~8.8 (3H, m)

2) MS: m/z 397 (M^+)

Ex. 115



N-(3-Phenylpropylaminoethyl)-2-(3-pyridyl)thiazolidine-4-carboxamide

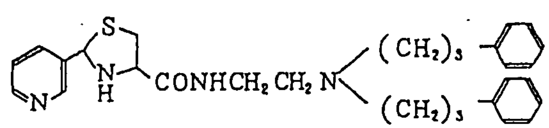
Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.45~2.16 (4H, m), 2.45~3.05 (6H, m), 3.10~3.75 (4H, m), 4.08~4.40 (1H, br), 5.36~5.70 (1H, br d, J=10Hz), 6.92~7.41 (6H, m), 7.53 (1H, br s), 7.68~7.96 (1H, m), 8.40~8.82 (2H, m)

2) MS: m/z 371 (M^++1)

Ex. 116



N-Di(3-phenylpropyl)aminoethyl-2-(3-pyridyl)thiazolidine-4-carboxamide

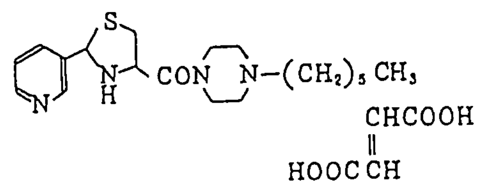
Physicochemical Properties

1) NMR ($CDCl_3$)

δ: 1.52~2.10 (5H, m), 2.32~2.75 (10H, m), 3.14~3.77 (4H, m), 4.15~4.40 (1H, m), 5.43 (0.7H, d, J=12Hz), 5.55 (0.3H, d, J=12Hz), 7.00~7.41 (11H, m), 7.41~7.93 (2H, m), 8.46~8.74 (2H, m)

2) MS: m/z 489 (M^++1)

Ex. 117



1-Hexyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

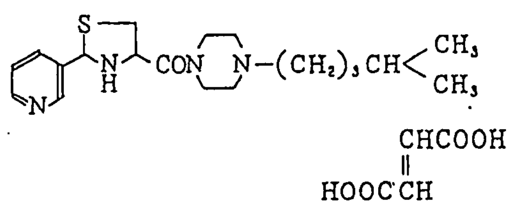
Physicochemical Properties

1) Melting point: 128°C

2) Elemental analysis (for $C_{23}H_{34}N_4O_5S$):

	C	H	N	S
Calculated: (%)	57.72	7.16	11.71	6.70
Found: (%)	57.60	7.22	11.61	6.61

Ex. 118



1-(4-Methylpentyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

Physicochemical Properties

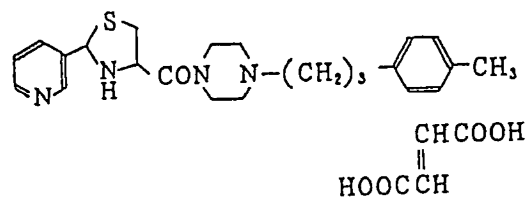
1) Melting point: 145~148°C

2) NMR (DMSO-d_6)

δ: 0.83 (6H, d, J=6Hz), 0.97~1.16 (5H, m), 2.24~2.76 (6H, m), 2.84~3.90 (6H, m), 4.29 (1H, q, J=7Hz), 5.58 (0.5H, s), 5.88 (0.5H, s), 6.61 (2H, s), 7.25~7.57 (1H, m), 7.75~8.08 (1H, m), 8.39~8.80 (2H, m)

3) MS: m/z 362 ($M^{+\cdot}-C_4H_4O_4$)

Ex. 119



1-[2-(3-Pyridyl)thiazolidin-4-ylcarbonyl]-4-[3-(p-tolyl)-propyl]piperazine fumarate

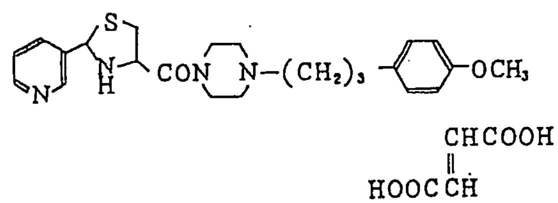
Physicochemical Properties

1) Melting point: 178~181°C

2) Elemental analysis (for $C_{27}H_{34}N_4O_5S$):

	C	H	N	S
Calculated: (%)	61.58	6.51	10.64	6.09
Found: (%)	61.20	6.47	10.52	6.26

Ex. 120



1-[3-(p-Methoxyphenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

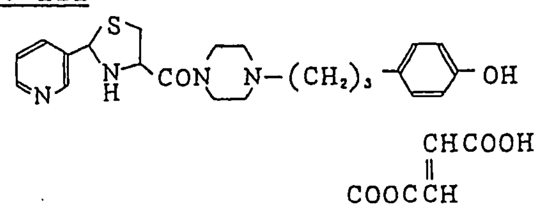
Physicochemical Properties

Melting point: 141~143°C

Elemental analysis (for $C_{27}H_{34}N_4O_6S$):

	C	H	N	S
Calculated: (%)	59.76	6.32	10.32	5.91
Found: (%)	59.50	6.31	10.28	5.98

Ex. 121



1-[3-(p-Hydroxyphenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-piperazine fumarate

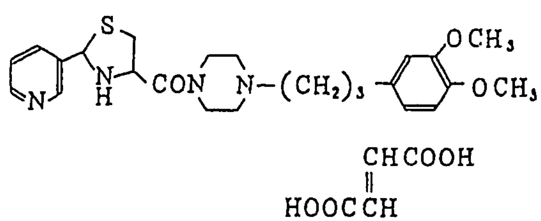
Physicochemical Properties

1) Melting point: 182~185°C

2) Elemental analysis (for $C_{26}H_{32}N_4O_6S$):

	C	H	N	S
Calculated: (%)	59.07	6.10	10.60	6.07
Found: (%)	58.68	6.03	10.44	6.07

Ex. 122



1-[3-(3,4-Dimethoxyphenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

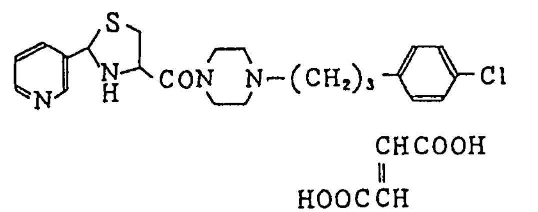
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.53~1.95 (2H, m), 2.20~2.68 (8H, m), 2.83~3.89 (6H, m), 3.72 (3H, s), 3.74 (3H, s), 4.28 (1H, q, J=7Hz), 5.55 (0.5H, s), 5.88 (0.5H, s), 6.65 (2H, s), 6.69~6.95 (3H, m), 7.25~7.51 (1H, m), 7.74~8.05 (1H, m), 8.39~8.74 (2H, m)

2) MS: m/z 457 ($M^{+}+1-C_4H_4O_4$)

Ex. 123



1-[3-(p-Chlorophenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

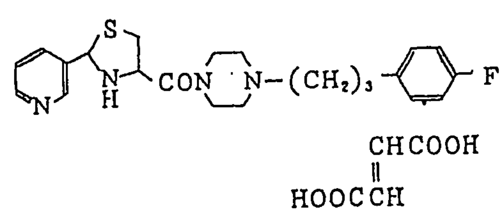
Physicochemical Properties

1) Melting point: 187~189°C

2) Elemental analysis (for $C_{26}H_{31}N_4O_5SCl$):

	C	H	N	Cl	S
Calculated: (%)	57.08	5.71	10.24	6.48	5.86
Found: (%)	57.27	5.77	10.17	6.20	5.82

Ex. 124



1-[3-(p-Fluorophenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

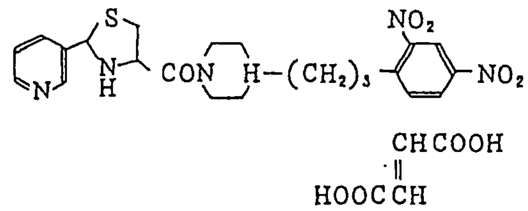
Physicochemical Properties

1) Melting point: 171~172°C

2) Elemental analysis (for $C_{26}H_{31}N_4O_5FS$):

	C	H	N	F	S
Calculated: (%)	58.85	5.89	10.56	3.58	6.04
Found: (%)	58.82	5.93	10.50	3.33	6.21

Ex. 125



1-[3-(2,4-Dinitrophenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

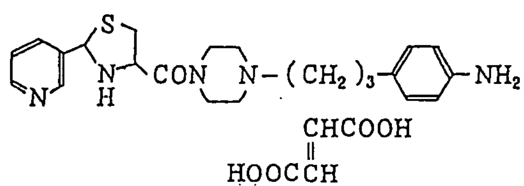
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.60~2.05 (2H, m), 2.19~2.66 (6H, m), 2.80~3.78 (8H, m), 4.10~4.42 (1H, m), 5.58 (0.5H, s), 5.89 (0.5H, s), 6.63 (2H, s), 7.26~7.57 (1H, m), 7.72~8.08 (2H, m), 8.35~8.84 (4H, m)

2) MS: m/z 487 ($M^{+}+1-C_4H_4O_4$)

Ex. 126



1-[3-(p-Aminophenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

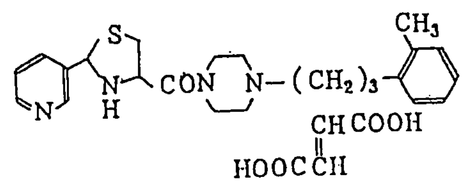
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.48~1.89 (2H, m), 2.18~2.68 (8H, m), 2.81~3.76 (6H, m), 4.16~4.43 (1H, m), 5.58 (0.5H, s), 5.89 (0.5H, s), 6.49 (1H, d, J=9Hz), 6.63 (2H, s), 6.83 (1H, d, J=9Hz), 7.25~7.52 (1H, m), 7.74~8.15 (1H, m), 8.41~8.81 (2H, m)

2) MS: m/z 411 ($M^{+}-C_4H_4O_4$)

Ex. 127



1-[3-(o-Methylphenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

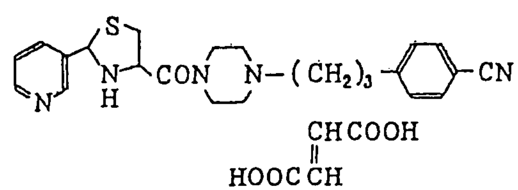
Physicochemical Properties

1) Melting point: 151~153°C

2) Elemental analysis (for $C_{27}H_{34}N_4O_5S$):

	C	H	N	S
Calculated: (%)	61.58	6.51	10.64	6.09
Found: (%)	61.33	6.41	10.58	6.10

Ex. 128



1-[3-(p-Cyanophenyl)propyl]-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

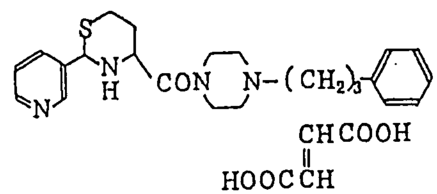
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.58~1.92 (2H, m), 2.16~2.80 (8H, m), 2.80~3.68 (6H, m), 4.12~4.42 (1H, m), 5.55 (0.3H, s), 5.87 (0.7H, s), 6.65 (2H, s), 7.25~7.53 (3H, m), 7.65~8.03 (3H, m), 8.36~8.73 (2H, m)

2) MS: m/z 421 ($M^+-C_4H_4O_4$)

Ex. 129



1-(3-Phenylpropyl)-4-[2-(3-pyridyl)-3,4,5,6-tetrahydro-2H-thiazin-4-yl-carbonyl]piperazine fumarate

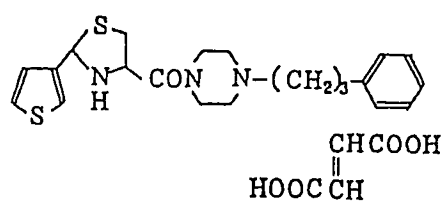
Physicochemical Properties

1) NMR (DMSO-d_6)

δ: 1.59~1.9 (4H, m), 2.2~2.8 (8H, m), 2.8~3.6 (6H, m), 3.9~4.2 (1H, m), 5.6 (1H, s), 6.66 (2H, s), 7.1~7.6 (6H, m), 7.6~8.0 (1H, m), 8.4~8.8 (2H, m)

2) MS: m/z 410 ($M^+-C_4H_4O_4$)

Ex. 130



1-(3-Phenylpropyl)-4-[2-(3-thienyl)thiazolidin-4-yl-carbonyl]piperazine fumarate

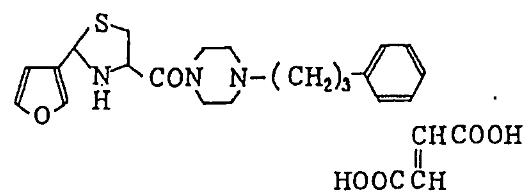
Physicochemical Properties

1) Melting point: 152~155°C (decomposition)

2) Elemental analysis (for $C_{25}H_{31}N_3O_5S_2$):

	C	H	N	S
Calculated: (%)	58.01	6.04	8.12	12.39
Found: (%)	58.04	6.04	8.11	12.62

Ex. 131



1-(3-Phenylpropyl)-4-[2-(3-furyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

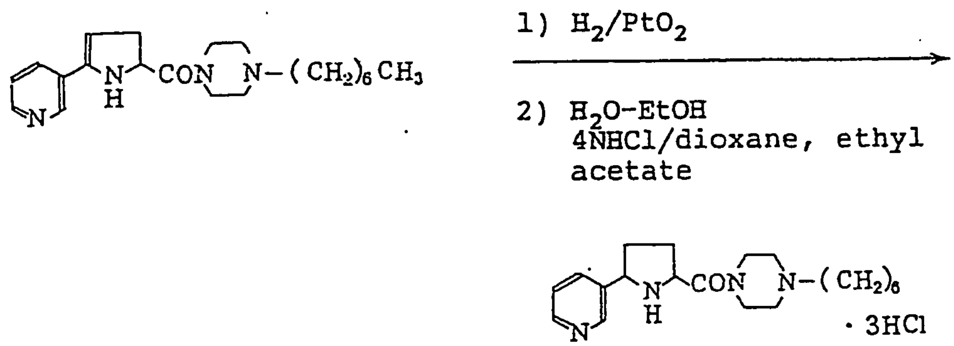
Physicochemical Properties

1) Melting point: 173~175°C

2) Elemental analysis (for $C_{25}H_{31}N_3O_6S$):

	C	H	N	S
Calculated: (%)	59.86	6.23	8.38	6.39
Found: (%)	59.76	6.14	8.37	6.47

EXAMPLE 132



1-Heptyl-4-[2-(3-pyridyl)-2-pyrrolin-5-ylcarbonyl]piperazine (570 mg) was catalytically reduced in 20 ml of water plus 20 ml of ethanol in the presence of platinum oxide as the catalyst until cessation of the absorption of hydrogen. The catalyst was filtered off, the filtrate was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (5 g). Elution with methanol-ethyl acetate (1:10, v/v) gave 250 mg of 1-heptyl-4-[5-(3-pyridyl)pyrrolidin-2-ylcarbonyl]piperazine. This product was converted to its trihydrochloride (180 mg) in the same manner as in Example 54. Melting point 138 143°C.

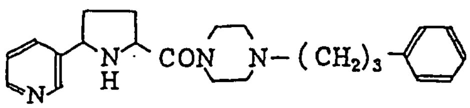
Elemental analysis (for $C_{21}H_{37}N_4OCl_3 \bullet 1.8H_2O$):

	C (%)	H (%)	N (%)	Cl (%)
Calculated:	50.41	8.18	11.20	21.26
Found:	50.49	7.83	11.09	21.10

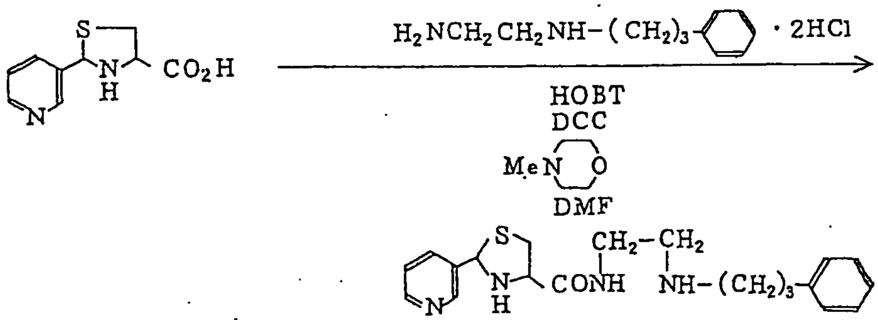
EXAMPLE 133

The following compound was obtained in the same manner as in Example 132 except that the treatment with a hydrogen chloride was not carried out.

Desired Product

Chemical Structure and Chemical Name	Physicochemical Properties
 ·3HCl 1-(3-Phenylpropyl)-4-[5-(3-pyridyl)pyrrolidin-2-ylcarbonyl]piperazine	1) NMR ($CDCl_3$) δ: 1.56~2.88 (15H, m), 3.43~ 3.90 (4H, m), 3.99~4.34 (2H, m), 7.04~7.44 (6H, m), 7.91 (1H, dt, J= 2Hz, J=8Hz), 8.53 (1H, dd, J=2Hz, J=5Hz), 8.65 (1H, d, J=2Hz). 2) MS: m/z 378 (M^+)

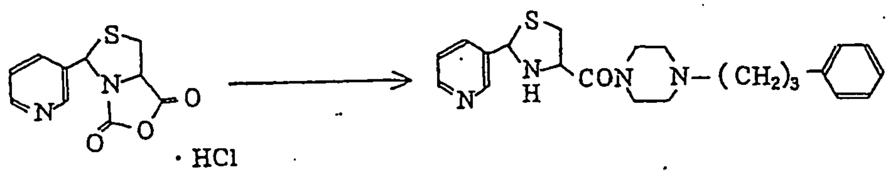
EXAMPLE 134



·2HCl

To a solution of 200 mg of 3-phenylpropylethylenediamine and 81 mg of N-methylmorpholine in 5 ml of dimethylformamide, there were added in sequence 120 mg of 1-hydroxybenzotriazole, 180 mg of dicyclohexylcarbondiimide and 170 mg of 2-(3-pyridyl)thiazolidine-4-carboxylic acid. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, the insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. After addition of 0.5 N aqueous sodium hydroxide, the residue was extracted with ethyl acetate. The organic layer was extracted with 1 N hydrochloric acid, and the aqueous layer was adjusted to pH 10 with potassium carbonate and extracted again with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to alumina column chromatography (20 g). Elution with methanol-ethyl acetate (1:10) gave 160 mg of N-(3-phenylpropylaminoethyl)-2-(3-pyridyl)thiazolidine-4-carboxamide. The NMR and MS data for this compound were in agreement with those given in Examples 115.

EXAMPLE 135



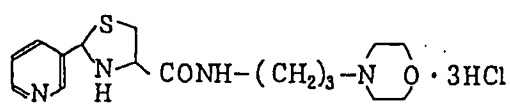
A solution of 40 mg of 1-(3-phenylpropyl)piperazine in 0.5 ml of dimethyl sulfoxide was added to a solution of 50 mg of 1,3-dioxo-5-(3-pyridyl)thiazolidino-[3,4-c]oxazolidine hydrochloride in 1 ml of dimethyl sulfoxide at room temperature. The reaction mixture was stirred for 2 hours at room temperature, then diluted with ethyl acetate, washed in sequence with saturated aqueous solution of sodium hydrogen carbonate, water and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 70 mg of 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine. The physicochemical properties of this product were in agreement with those of the compound of Example 108.

EXAMPLE 136

The following compound was obtained in the same manner as in Example 135.

Desired Product

Chemical Structure and Chemical Name



N-(3-morpholinopropyl)-2-(3-pyridyl)thiazolidine-4-carboxamide trihydrochloride

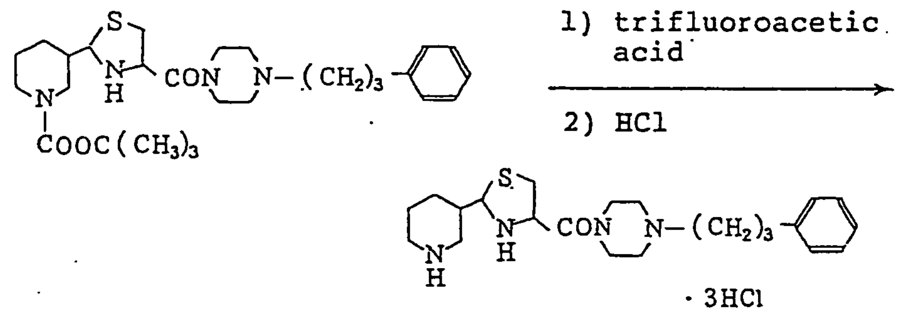
Physicochemical Properties

1) Melting point: 92~96°C

2) Elemental analysis
(for $C_{16}H_{27}N_4O_2SCl_3 \cdot 1.5\ H_2O$):

	C	H	N	S	Cl
Calculated: (%)	40.64	6.39	11.85	6.78	22.49
Found: (%)	40.72	6.12	11.58	6.90	22.62

EXAMPLE 137

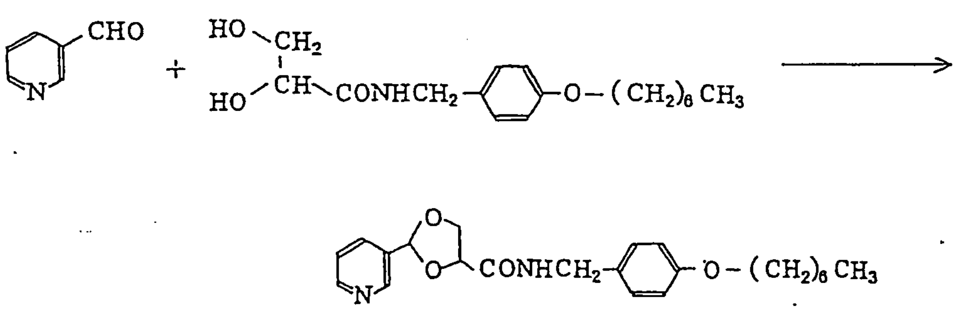


1-[2-(1-tert-Butoxycarbonyl-3-piperidinyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine (430 mg) was dissolved in 3 ml of dichloromethane, followed by addition of 2 ml of trifluoroacetic acid. The mixture was stirred at room temperature for 6 hours. The reaction mixture was poured into 60 ml of saturated aqueous solution of sodium hydrogen carbonate, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 280 mg of 1-(3-phenylpropyl)-4-[2-(3-piperidinyl)thiazolidin-4-ylcarbonyl]piperazine. This compound was dissolved in 8 ml of ethyl acetate, and 1 ml of 4 N hydrogen chloride solution in dioxane was added. After 30 minutes of stirring, the resultant solid was collected by filtration and dried to give 200 mg of 1-(3-phenylpropyl)-4-[2-(3 piperidinyl)thiazolidin-4-ylcarbonyl]piperazine trihydrochloride. Melting point 174-178°C.

Elemental analysis (for $C_{22}H_{37}N_4OSCl_3 \cdot 1.5H_2O$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	49.02	7.48	10.39	5.95
Found:	49.02	7.40	10.29	6.00

EXAMPLE 138



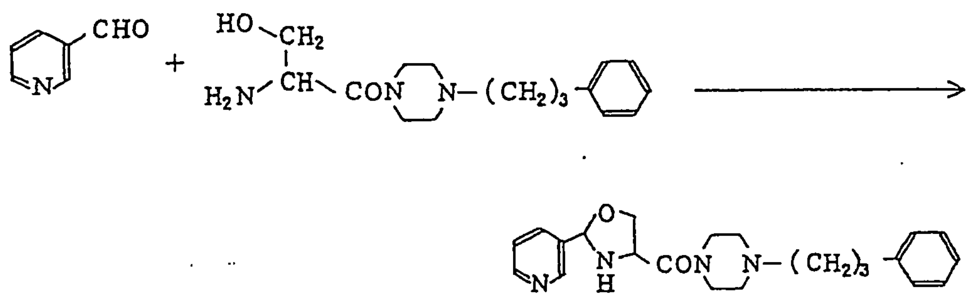
p-Toluenesulfonic acid (5 mg) was added to a solution of 70 mg of N-(p-heptyloxybenzyl)glyceramide and 50 mg of pyridine-3-carboxaldehyde in 70 ml of benzene plus 2.5 ml of pyridine, and the mixture was refluxed for 12 hours for azeotropic dehydration. After cooling, the reaction mixture was washed with two portions of saturated aqueous solution of sodium hydrogen carbonate, three portions of water and one portion of saturated aqueous solution of sodium chloride, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue obtained was purified by preparative silica gel thin layer chromatography to give 60 mg of N-(p-heptyloxybenzyl)-2-(3-pyridyl)-1,3-dioxolane-4-carboxamide.

NMR ($CDCl_3$)

δ: 0.90 (3H, br t), 1.2~1.5 (8H), 1.6~2.0 (2H), 3.95 (2H, t, J=7Hz), 4.1~4.8 (5H), 5.89 and 5.99 (respectively

1H), 6.6~7.2 (1H, exchange with D_2O), 6.8~7.4 (5H), 7.6~7.8 (1H), 8.6~8.7 (2H)
MS: m/z 398 (M^+)

EXAMPLE 139



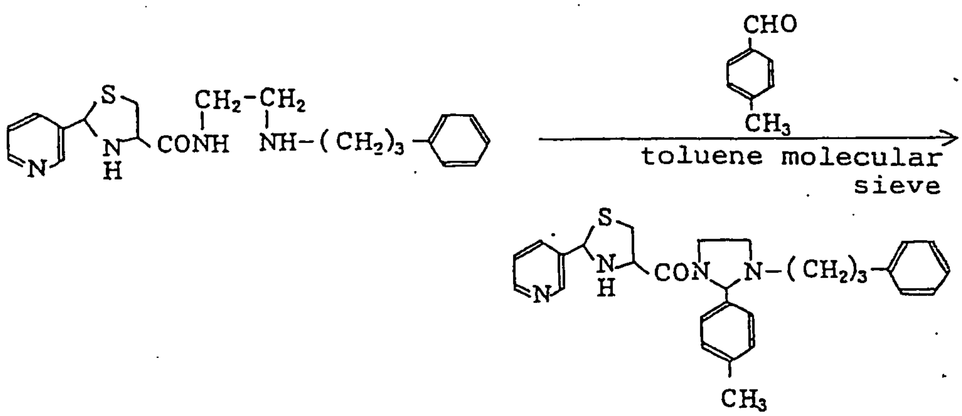
1-(3-Phenylpropyl)-4-[2-(3-pyridyl)oxazolidin-4-ylcarbonyl]piperazine was obtained from 1-(2-amino-3-hydroxypropionyl)-4-(3-phenylpropyl)piperazine and pyridine-3-carboxaldehyde by following the procedure of Example 138. Yield, 50%.

Elemental analysis (for $C_{22}H_{28}N_4O_2$):

	C (%)	H (%)	N (%)
Calculated:	69.45	7.42	14.72
Found:	69.16	7.38	14.58

MS: m/z 380 (M^+)

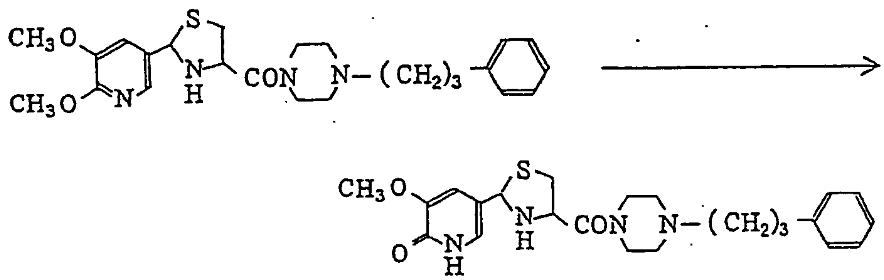
EXAMPLE 140



A mixture of 50 mg of N-(3-phenylpropylaminoethyl)-2-(3-pyridyl)thiazolidine-4-carboxamide, 17 mg of p-tolualdehyde, 100 mg of molecular sieve (4A) and 2 ml of toluene was heated in a sealed tube at 120°C for 8 hours. the reaction mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was subjected to preparative thin layer chromatography (development with 2% methanol-ethyl acetate being made twice; R_f value=0.15) to give 3.3 mg of 1-(3-phenylpropyl)-3-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]-2-(4-tolyl)imidazolidine.

NMR ($CDCl_3$)
δ: 1.55~1.93 (3H, m), 2.39 (3H, s), 2.42~2.87 (8H, m), 3.09 (1H, dd, J=8Hz, 12Hz), 3.41 (1H, dd, J=4Hz, J=12Hz), 4.07~4.30 (1H, m), 5.16 (1H, s), 5.52 (1H, s), 7.03~7.42 (10H, m), 7.60~7.81 (1H, m), 8.44 (1H, dd, J=2Hz, J=5Hz), 8.63 (1H, d, J=2Hz)
MS: m/z 472 (M^+)

EXAMPLE 141



1-[2-(5,6-Dimethoxy-3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine (730 mg) was dissolved in 25 ml of ethyl acetate. To the solution was added with stirring at room temperature 2 N hydrogen chloride solution in dioxane. The resultant powder was collected by filtration and dissolved in saturated sodium carbonate solution. Ethyl acetate was added, the organic layer was separated and washed with water, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 25 ml; 10% methanol ethyl acetate) to give 210 mg of 1-[2-(5-methoxy-6-oxo-5,6-dihydro-3-pyridyl)thiazolidin-4-ylcarbonyl]-4-(3-phenylpropyl)piperazine.

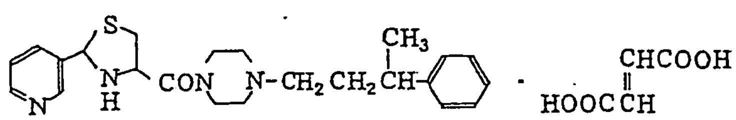
NMR (DMSO-d_6)

δ: 1.56 ~ 1.94 (2H, m), 2.20 ~ 2.80 (8H, m), 2.90 ~ 4.40 (10H, m), 5.28 ~ 5.66 (1H, m), 6.80 ~ 7.44 (7H, m)

MS: m/z 442 (M^+)

EXAMPLE 142

The following compound was obtained in the same manner as in Example 90.



1-(3-phenylbutyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine fumarate

Melting point 166-168°C

Elemental analysis (for $C_{27}H_{34}N_4O_5S$):

	C (%)	H (%)	N (%)	S (%)
Calculated:	61.58	6.51	10.64	6.09
Found:	61.21	6.45	10.58	6.42

MS: (m/z) 410 (M^+-$C_4H_4O_4$)

EXAMPLE 143

Tablet composition (per tablet)

The product obtained in Example 91		20 mg
Lactose		57 mg
Corn starch		38 mg
Hydroxypropylcellulose		4 mg
Magnesium stearate		1 mg
	Total	120 mg

A homogeneous mixture is prepared from 20 g of the product obtained in Example 91, 57 g of lactose and 38 g of corn starch. Then, 40 g of 10% hydroxypropylcellulose solution is added, and the mixture is subjected to wet granulation. The granules are forced through a sieve and then dried. One gram of magnesium stearate is added to the thus-obtained granulation product. After thorough mixing, the mixture is formed into tablets using a tableting machine (die-punch size: 7 mm, 5.6 R).

EXAMPLE 144

Capsule composition (per capsule)

The product obtained in Example 91		15 mg
Crystalline cellulose		40 mg
Crystalline lactose		144 mg
Magnesium stearate		1 mg
	Total	200 mg

A homogeneous mixture is prepared from 15 g of the product obtained in Example 91, 40 g of crystalline cellulose, 144 g of crystalline lactose and 1 g of magnesium stearate and filled into No. 3 capsules using a capsule-filling machine.

EXAMPLE 145

Lyophilized preparation composition (per vial)
The fumarate obtained in Example 91   1 mg
D-Mannitol   5.0 mg

In 800 ml of water are dissolved 1 g of the product obtained in Example 91 and 50 g of D-mannitol in that order. Water is added to make the whole volume 1 liter. This solution is aseptically filtered, then filled in 1-ml portions into vials, and lyophilized.

The anti-PAF activity of the compounds according to the invention has been confirmed by the following test:
Effect on platelet activating factor (PAF)-induced platelet aggregation in plasma
Method: Nine volumes of blood were drawn from the central ear artery of a male rabbit (Japan white, 3 kg) directly into a plastic syringe containing 1 volume of 3.8% sodium citrate. The blood was centrifuged at 270 × g for 10 minutes at room temperature and the platelet rich plasma (PRP) was removed. The pellet was further centrifuged at 1,100 × g for 15 minutes. The supernatant was used as platelet poor plasma (PPP). The platelet concentration was adjusted to 5×10^5 cells/µl with PPP. Platelet aggregation was measured by the method of G.V.R. Born and M.J. Cross [Journal of Physiology, 168, 178-195 (1963)] using a HEMA TRACER (Nikou Bio Science, Japan). Varying concentrations of compounds were added to the PRP 2 minutes prior to PAF (10^{-8}

M). The extent of platelet aggregation was determined by the maximum change of light transmission, taking the transmission of unstimulated PRP to be 0% and that of PPP to be 100%. Percent inhibition by added compound was calculated by dividing the percent aggregation in the presence of the compound by that in the control, and then the IC_{50} values were calculated.

Results: As shown in Table 1, many compounds of the present invention inhibited the PAF-induced rabbit platelet aggregation in plasma (IC_{50} value of at least 10^{-5} M). Especially, the compounds of Examples 37, 49, 67, 71, 81, 83, 85, 90, 91, 119 and 142 were potent inhibitors having IC_5 values of 2.8×10^{-8} to 8.5×10^{-8} M, while these compounds did not inhibit the platelet aggregation induced by ADP (3×10^{-6} M), arachidonic acid (1×10^{-4} M) or collagen (10 µg/ml) (data not shown). These results suggest that the compounds of this invention are specific antagonists of PAF.

Table 1

Example No.	IC_{50} (µM)
20	0.8
22	0.790
23	0.430
24	0.250
32	0.490
34	0.950
36	0.860
37	0.054

Table 1 (cont'd)

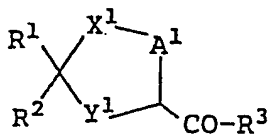
Example No.	IC_{50} (μM)
46	0.650
48	0.450
49	0.085
50	0.800
54	0.240
55	0.160
56	0.120
57	0.200
58	0.390
59	0.210
60	0.760
61	0.770
63	0.500
64	0.390
65	0.120
66	0.430
67	0.071
71	0.064
72	0.900
76	0.900
77	0.430
78	0.280
80	0.340
81	0.028

Table 1 (cont'd)

Example No.	IC_{50} (μM)
82	0.160
83	0.034
84	0.220
85	0.072
89	0.400
90	0.067
91	0.071
92	0.260
93	0.630
97	0.120
105	0.940
117	0.260
118	0.630
119	0.079
120	0.170
121	0.19
123	0.18
124	0.18
125	0.45
126	0.18
127	0.46
128	0.97

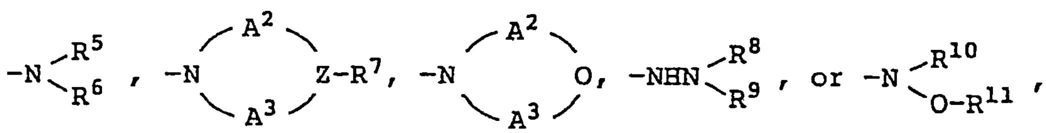
Claims

1. A saturated heterocyclic carboxamide derivative of the general formula (I) or a salt thereof:



(I)

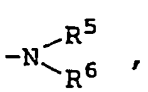
wherein R^1 represents a substituted or unsubstituted 5 or 6-membered heterocyclic group which may be condensed with a benzene ring; R^2 represents a hydrogen atom, a lower alkyl group, or an R^1 group defined above; X^1 represents an oxygen or sulfur atom or a methylene group which may be substituted by a lower alkyl group; Y^1 represents an oxygen or sulfur atom or a group of formula $>N-R^4$ wherein R^4 is a hydrogen atom or a lower alkyl, carboxyl, acyl or (lower alkoxy)carbonyl group; A^1 represents a methylene or ethylene group which may be substituted by a lower alkyl group(s); R^3 represents a group of formula

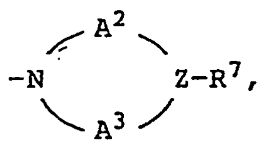
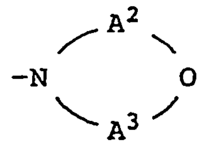
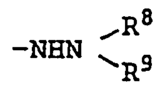


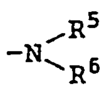
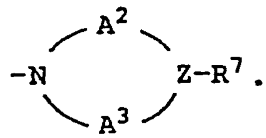
in which one of R^5 and R^6 is a hydrogen atom or a substituted or unsubstituted hydrocarbon group and the other is a substituted or unsubstituted hydrocarbon group or a substituted or unsubstituted 5- or 6-membered heterocyclic group which may be condensed with a benzene ring, A^2 and A^3, are the same or different and selected from substituted and unsubstituted lower alkylene groups, Z is a methine group ($>CH-$) or a nitrogen atom, R^7 is a hydrogen atom, a substituted or unsubstituted hydrocarbon group or a carboxyl, acyl, (lower alkoxy)carbonyl, carbamoyl, or mono- or di-(lower alkyl)aminocarbonyl group, and R^8, R^9, R^{10} and R^{11}, are the same or different and selected from a hydrogen atom and lower alkyl, aralkyl and aryl groups.

2. A compound as claimed in claim 1, wherein R^1 is a pyridyl (optionally in pyridone form), quinolyl, pyrrolyl, piperidyl, a pyrazinyl, or furyl group, which may be substituted by one or two substituents selected from lower alkyl, lower alkoxy, (lower alkoxy)carbonyl and dimethylamino groups;

R^2 is a hydrogen atom or a lower alkyl or pyridyl group; X^1 is a sulfur or oxygen atom or a methylene group; Y^1 is an oxygen atom or $>N-R^4$ wherein R^4 is a hydrogen atom or a lower alkyl, an acyl or a (lower alkoxy)carbonyl group; A^1 is a methylene or ethylene group which may be substituted by one or two lower alkyl groups; and R^3 is

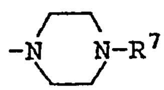


, , or , preferably

 or .

3. A compound as claimed in Claim 2 wherein R^1 is a pyridyl group which may be substituted by one or two substituents selected from lower alkyl, (lower alkoxy) carbonyl and dimethylamino groups; R^2 is a hydrogen atom: X^1 is a sulfur atom; Y^1 is $>N\text{-}R^4$; and A^1 is a methylene group which may be substituted by one or two lower alkyl groups.

4. A compound as claimed in Claim 3 wherein R^1 is a pyridyl group; R^2 is a hydrogen atom; X^1 is a sulfur atom; Y^1 is $>NH$; A^1 is a methylene group; and R^3 is

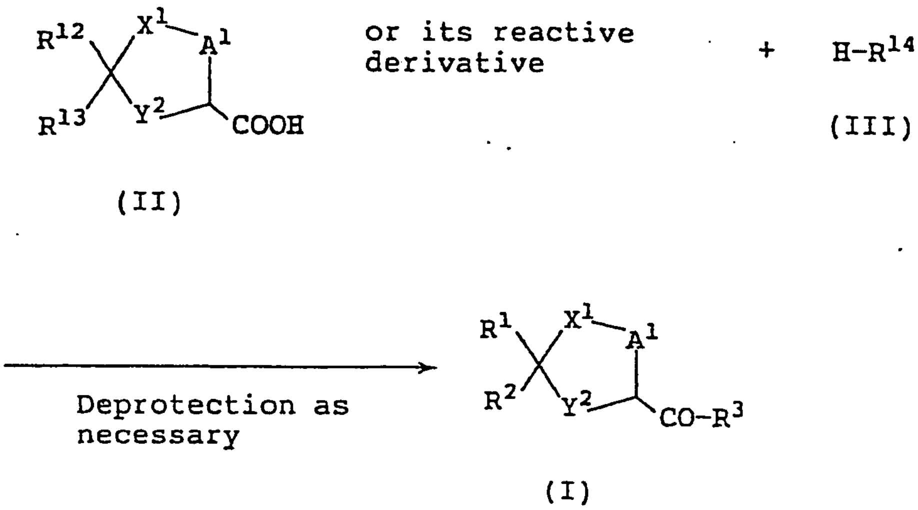
,

in which R^7 is an aryl-lower alkyl group.

5. A compound as claimed in Claim 1, which is 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine or an acid addition salt thereof;
1-decyl-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine or an acid addition salt thereof; or
1-(4-oxo-4-phenylbutyl)-4-[2-(3-pyridyl)thiazolidin-4-ylcarbonyl]piperazine or an acid addition salt thereof.

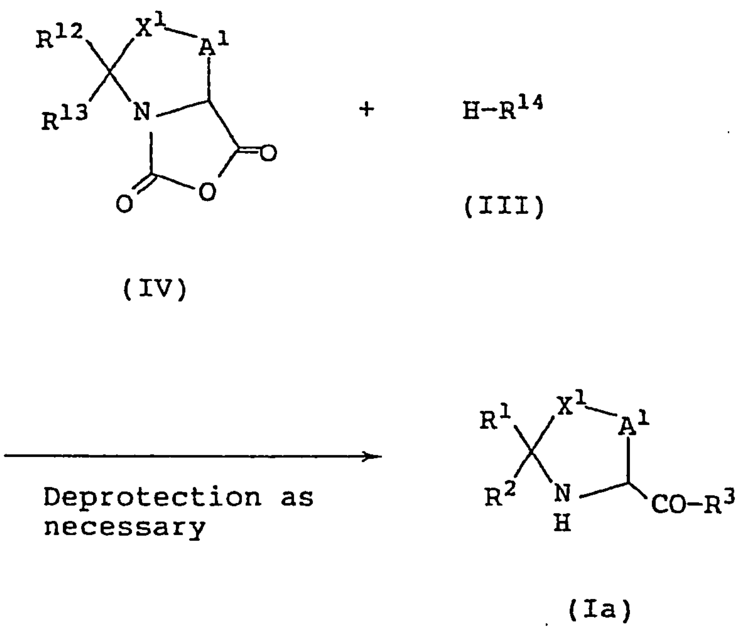
6. A process for producing a compound according to claim 1, which is one of Processes 1 to 17 below, optionally followed by conversion to or from salt form :

Process 1 (Amidation A)



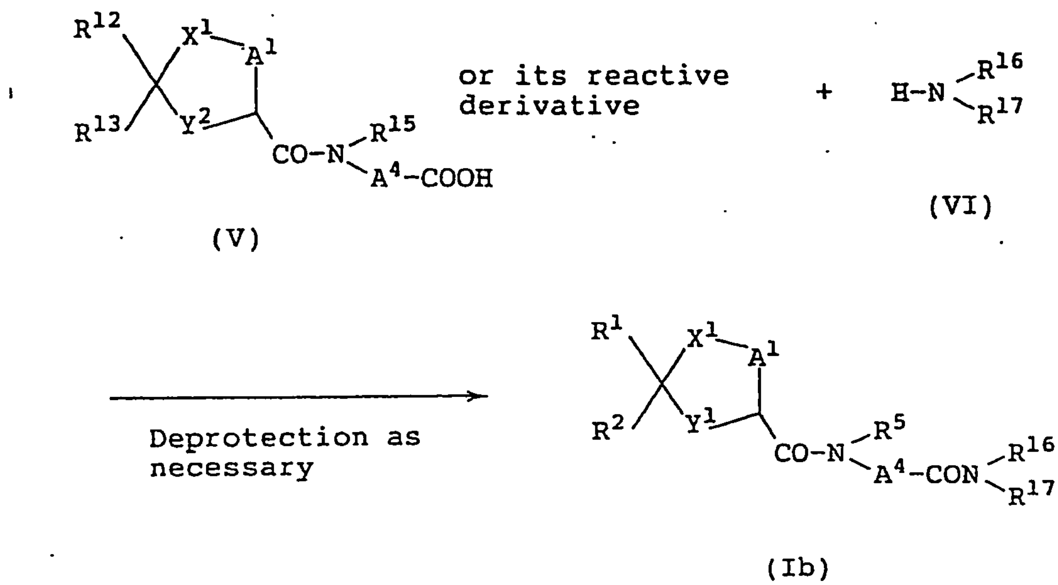
(II) (III) (I)

Process 2 (Amidation B)

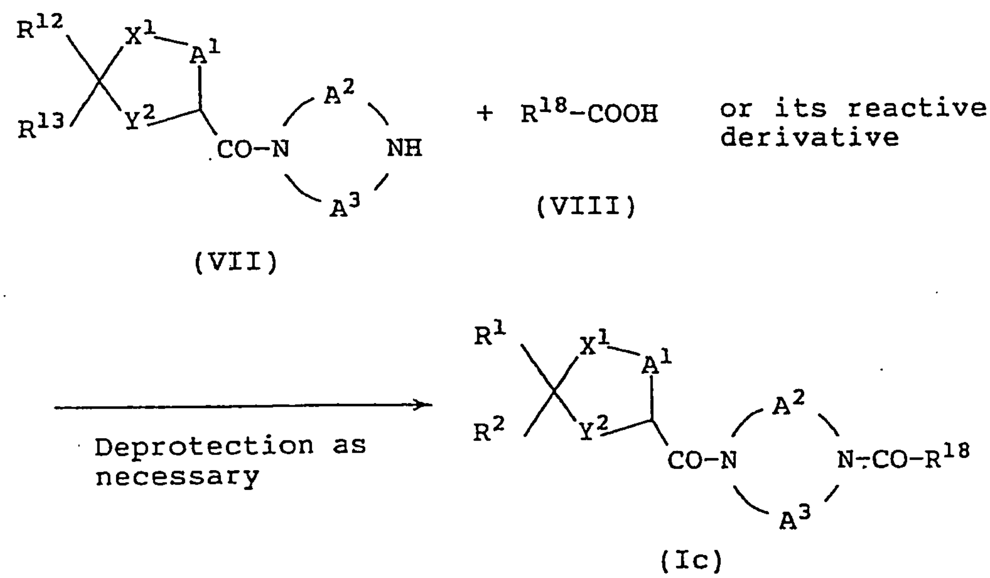


(IV) (III) (Ia)

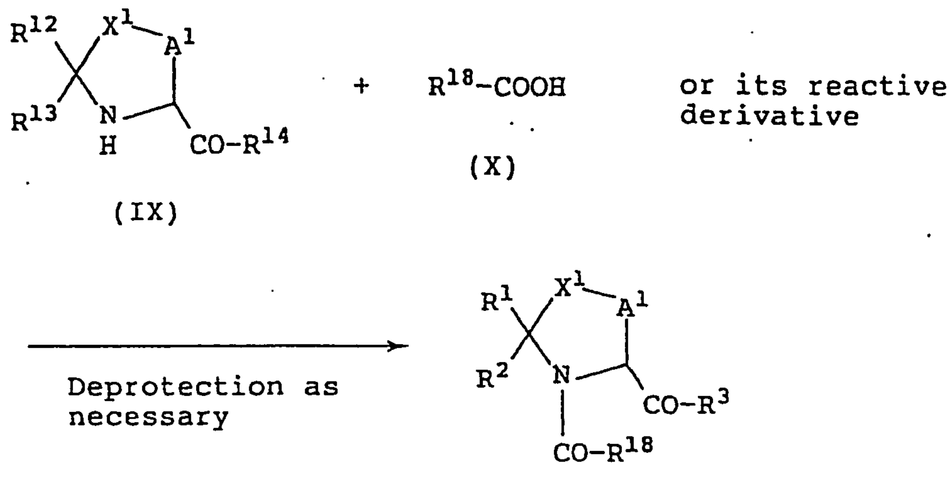
Process 3 (Amidation C)



Process 4 (N-Acylation A)

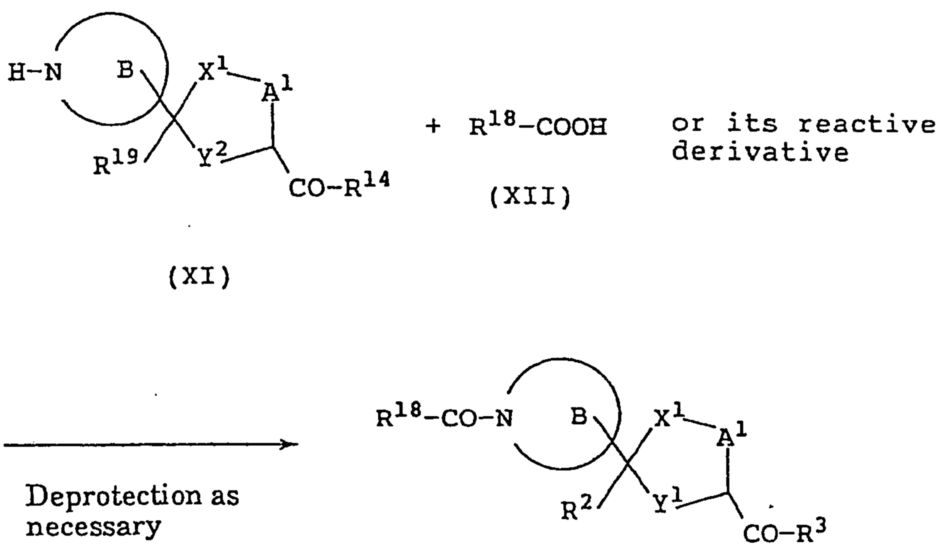


Process 5 (N-Acylation B)



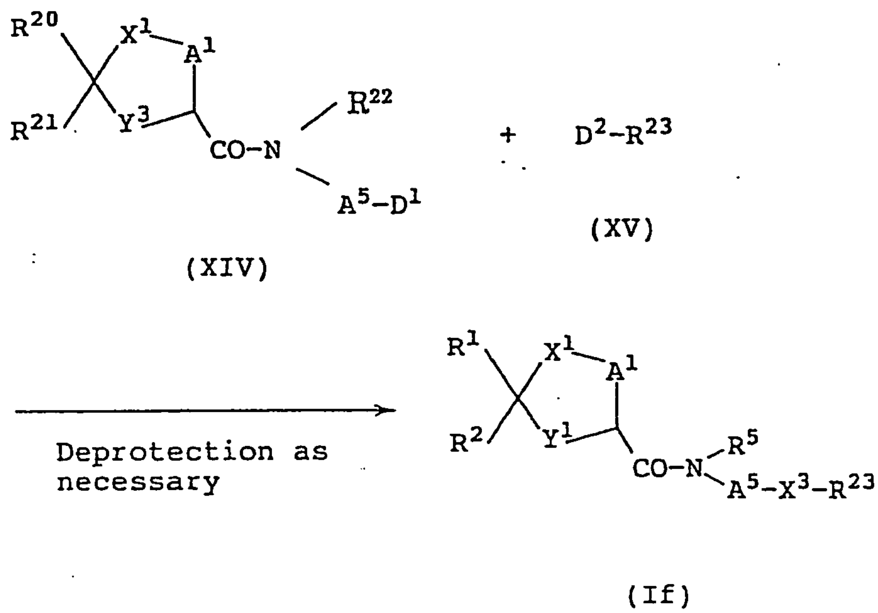
(IX) (X) (Id)

Process 6 (N-Acylation C)

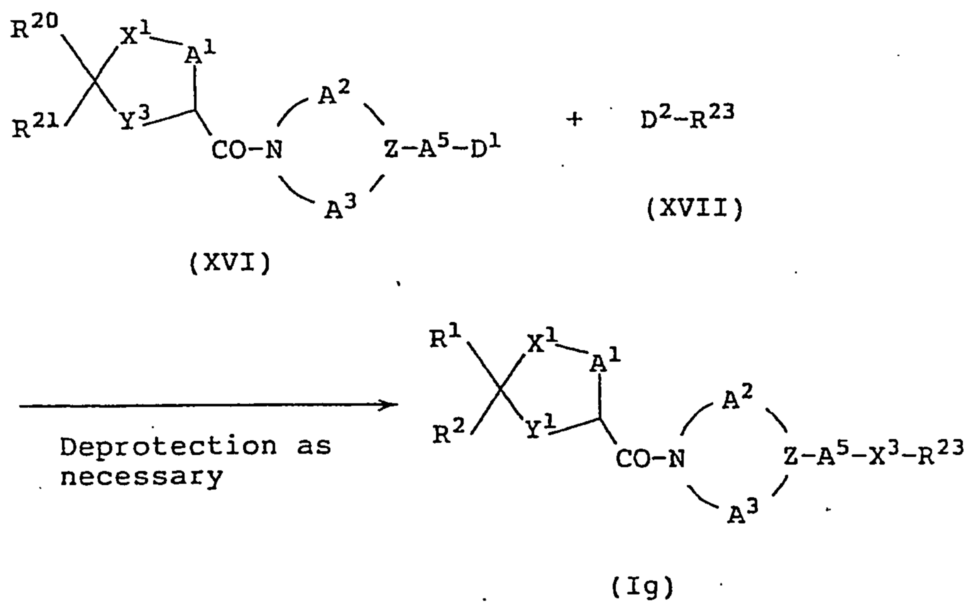


(XI) (XII) (Ie)

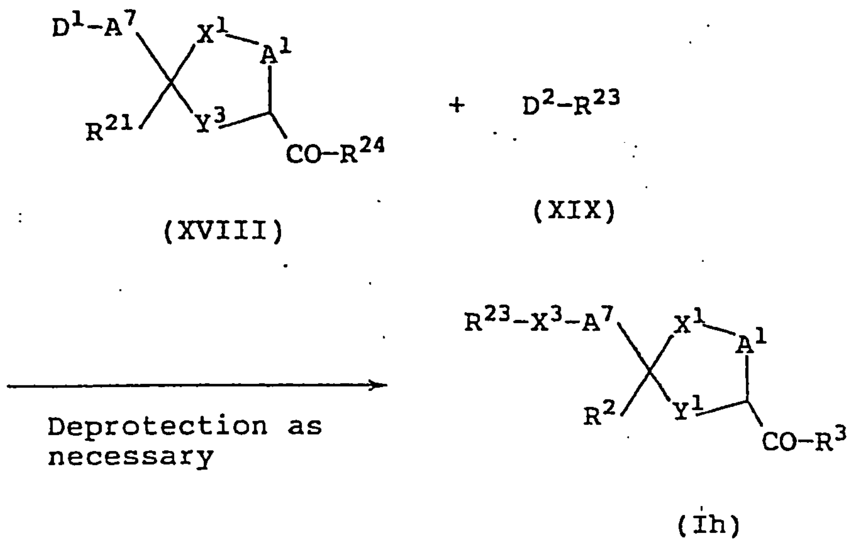
Process 7 (Etherification or thioetherification A)



Process 8 (Etherification or thioetherification B)

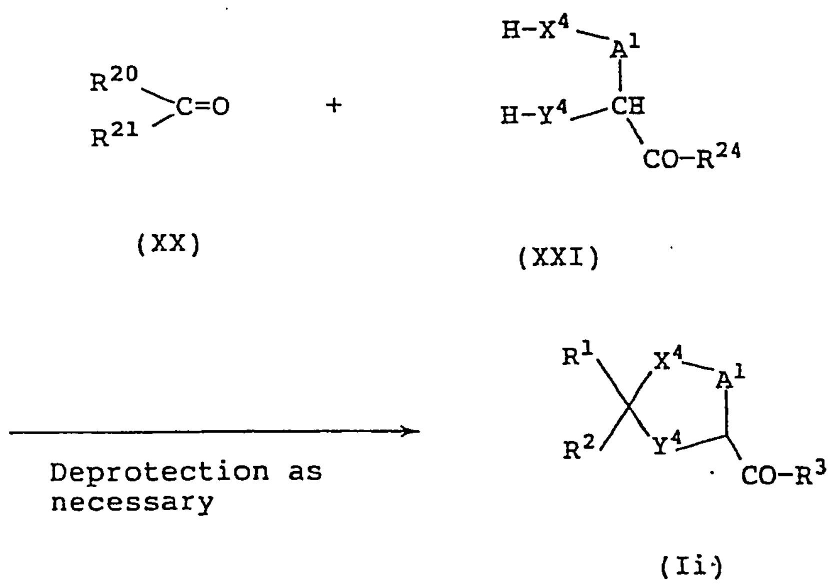


Process 9 (Etherification or thioetherification C)



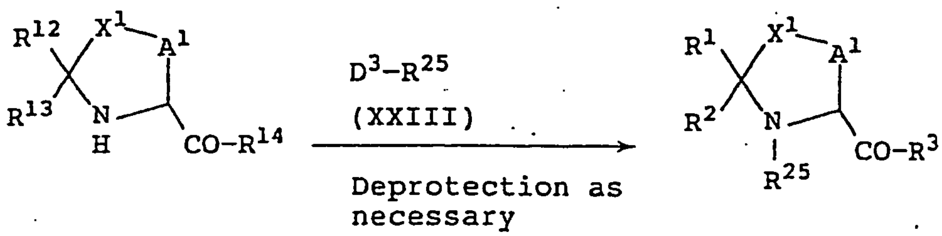
(XVIII) (XIX) (Ih)

Process 10 (Cyclization)



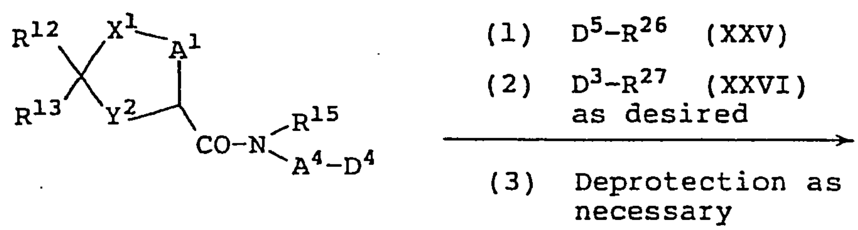
(XX) (XXI) (Ii)

Process 11 (N-Alkylation A)

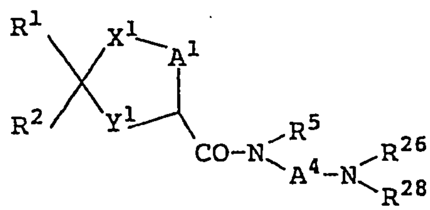


(XXII) (Ij)

Process 12 (N-Alkylation B)

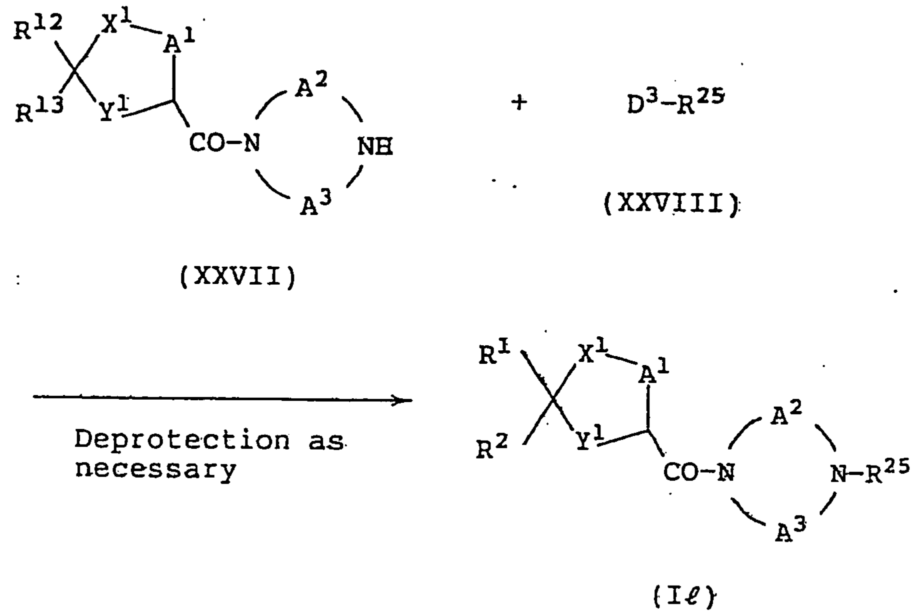


(XXIV)

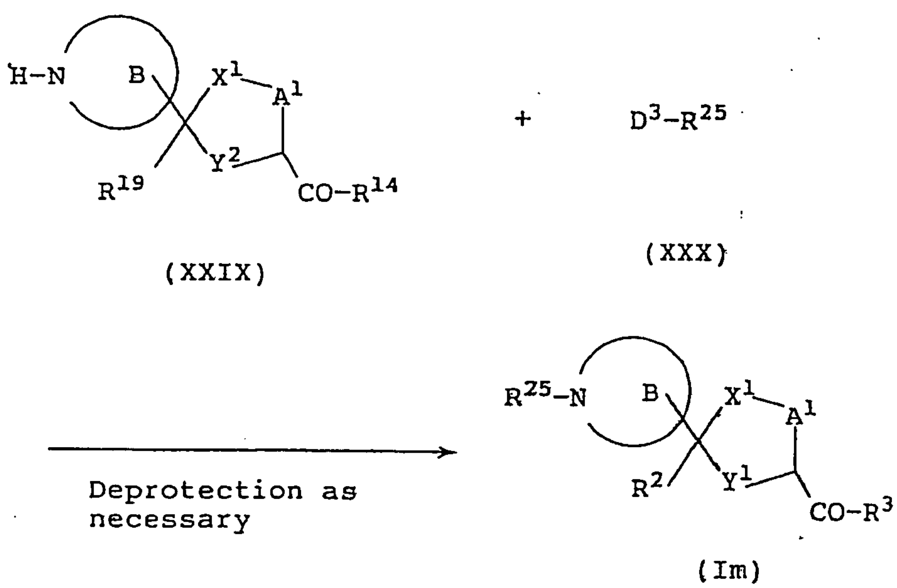


(Ik)

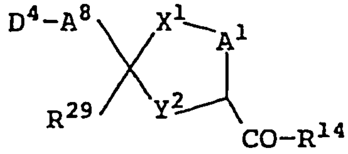
Process 13 (N-Alkylation C)



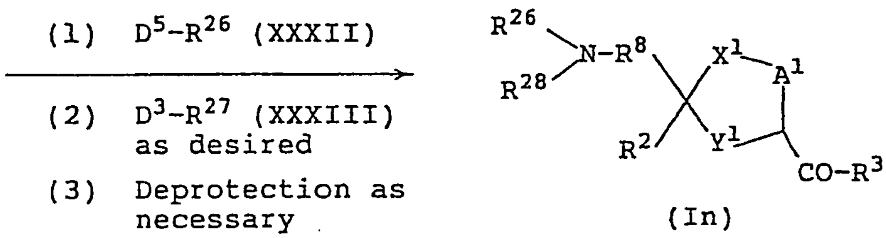
Process 14 (N-Alkylation D)



Process 15 (N-Alkylation E)

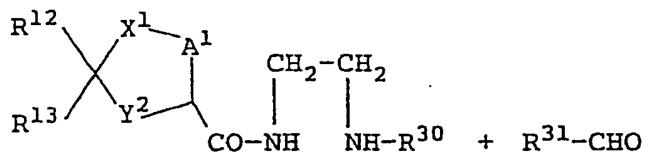


(XXXI)

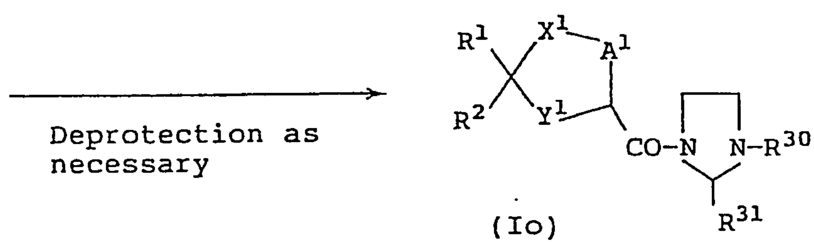


(In)

Process 16

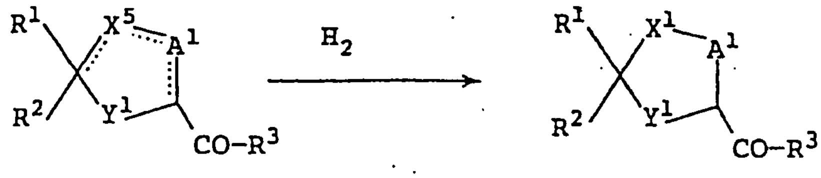


(XXXIV) (XXXV)



(Io)

Process 17 (Reduction)



(XXXVI) (Ip)

wherein R^1, R^2, R^3, R^4, R^5, X^1, A^1, Y^1 and Z are as defined in claim 1 and the other substituents are defined as follows:

R^{12}: the same group as R^1, which however may have a protective group;
R^{13} the same group as R^2, which however may have a protective group;
Y^2: the same group as Y^1, which however may have a protective group;
R^{14}: the same group as R^3, which however may have a protective group;
R^{15}: the same group as R^5, which however may have a protective group;
A^4: a divalent hydrocarbon group;
R^{16} and R^{17}: a hydrogen atom or a lower alkyl group; R^{16} and R^{17}, which may be the same or different, a hydrogen atom or a lower alkyl group;
R^{18}: the residue of an acyl group after removal of the carbonyl group therefrom;
: a nitrogen containing 5- or 6-membered heterocyclic group in which the nitrogen atom is not a tertiary one and which may be condensed with a benzene ring;
R^{19}: a hydrogen atom, a lower alkyl group or a group of the formula ,
R^{20}: the same group as R^1, which however may have a protective group;
R^{21}: the same group as R^2, which however may have a protective group;
Y^3: the same group as Y^1, which however may have a protective group;
R^{22}: the same group as R^5, which however may have a protective group;
A^5: the same group as A^4 or a divalent group of the formula A^4-X^2-A^6-;
X^2: an oxygen atom or a sulfur atom;
A^6: a lower alkylene group;
D^1 and D^2: one is a hydroxy group, a mercapto group, or an alkali metal-substituted hydroxy or mercapto group and the other is a halogen atom or an organo sulfonyloxy group;
R^{23}: an alkyl group of 1 to 10 carbon atoms, a cycloalkyl-lower alkyl group, an aralkyl group, an aryl group, an aryloxy-lower alkyl group or arylthio-lower alkyl group;
X^3: an oxygen atom or a sulfur atom;
A^7: a divalent 5- or 6-membered heterocyclic group, which may be condensed with a benzene ring, or a group of the formula -A^6-X^2-A^8-;
A^8: a divalent 5- or 6-membered heterocyclic group, which may be condensed with a benzene ring;
R^{24}: the same group as R^3, which however may have a protective group;
X^4: an oxygen atom or a sulfur atom;
Y^4: an oxygen atom, a sulfur atom or an imino group (-NH-);
D^3: a halogen atom or an organo sulfonyloxy group;
R^{25}: a lower alkyl group, a (lower alkoxy)carbonyl group or an acyl group;
D^4 and D^5: one is an amino group, which may have a protective group, and the other is a halogen atom or an organo sulfonyloxy group;
R^{26}: a hydrogen atom, a lower alkyl group or an aralkyl group when D^5 is an amino group which may have a protective group; a lower alkyl group or an aralkyl group when D^5 is a halogen atom or an organo sulfonyloxy acid group; D^5-R^{26} may be potassium phthalamide, provided that D^4 is a halogen atom or an organo sulfonyloxy group;
R^{27}: a lower alkyl group or an aralkyl group, which may be the same as or different from R^{26};
R^{28}: a hydrogen atom or the same group as R^{26} or R^{27};
R^{29}: a hydrogen atom, a lower alkyl group or a group of the formula D^4-A^8-;
R^{30}: a hydrogen atom, a lower alkyl group or an aralkyl or an aryl group;
R^{31}: a hydrogen atom, a lower alkyl group, an aralkyl group or an aryl group;
X^5: an oxygen or a sulfur atom, a methylene group which may have a lower alkyl group as a substituent or a methine group which may have a lower alkyl group as a substituent (i.e. H- or lower alkyl- C = or H- or lower alkyl- C -); and
---: one bond is a double bond.

7. A pharmaceutical composition containing at least one compound according to claim 1.

8. The use of a compound according to claim 1 for the preparation of a medicament having anti-PAF activity.

9. The intermediate compounds which are the products of the foregoing Reference Examples.

10. An intermediate compound selected from those of formula II, IV, V, VII, IX, XI, XIV, XVI, XVIII, XXII, XXIV, XXVII, XXIX, XXXI, XXXIV and XXXVI hereinbefore, or a salt thereof.